Risk of Invasive Cutaneous Squamous Cell Carcinoma After Different Treatments for Actinic Keratosis
A Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE Treatment of actinic keratosis (AK) aims to prevent cutaneous squamous cell carcinoma (cSCC). However, whether AK can progress into invasive cSCC is a matter of debate, and little is known about the effect of treatment on preventing cSCC.

OBJECTIVES To evaluate the risk of invasive cSCC and factors that may contribute to increased risk in patients with multiple AKs.

DESIGN, SETTING, AND PARTICIPANTS In this secondary analysis of a multicenter randomized clinical trial, 624 patients with a minimum of 5 AKs within an area of 25 to 100 cm² on the head were recruited from the Department of Dermatology of 4 hospitals in the Netherlands. Long-term follow-up was performed from July 1, 2019, to December 31, 2020.

INTERVENTIONS Patients were randomized to treatment with 5% fluorouracil, 5% imiquimod cream, methylaminolevulinate photodynamic therapy, or 0.015% ingenol mebutate gel.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of patients with invasive cSCC in the target area during follow-up. Secondary outcomes were the associations between risk of invasive cSCC and a priori defined potential prognostic factors, including type of treatment, severity of AK (Olsen grade), history of nonmelanoma skin cancer, and additional treatment.

RESULTS Of the 624 patients (558 [89.4%] male; median age, 73 years [range, 48-94 years]) in the study, 26 were diagnosed with a histologically proven invasive cSCC in the target area during follow-up. The total 4-year risk of developing cSCC in a previously treated area of AK was 3.7% (95% CI, 2.4%-5.7%), varying from 2.2% (95% CI, 0.7%-6.6%) in patients treated with fluorouracil to 5.8% (95% CI, 2.9%-11.3%) in patients treated with imiquimod. In patients with severe AK (Olsen grade III), the risk was 20.9% (95% CI, 10.8%-38.1%), and the risk was especially high (33.5%; 95% CI, 18.2%-56.3%) in patients with severe AK who needed additional treatment.

CONCLUSIONS AND RELEVANCE In this secondary analysis of a randomized clinical trial, risk of invasive cSCC was highest in patients with Olsen grade III AK and was substantially increased in patients who received additional treatment. These patients should be closely followed up after treatment.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02281682

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Actinic keratosis (AK) has an estimated prevalence worldwide that ranges from 11% to 60% and is a disease frequently diagnosed and treated by dermatologists and general practitioners. Several field-directed therapies for AK are available. The most important reason for treatment is the supposed reduction of the risk of developing invasive cutaneous squamous cell carcinoma (cSCC). However, whether AK can really progress to invasive cSCC is a matter of debate, and evidence about good indicators for the lesions at risk is scarce. Furthermore, there is limited evidence that treatment of AK decreases the risk of invasive cSCC development. In a recently published randomized clinical trial, patients who were supposed to have a high risk of SCC because of substantial sun exposure and a history of at least 2 keratinocyte carcinomas were empirically treated with fluorouracil as a chemoprevention strategy. Topical fluorouracil treatment significantly reduced the risk of cSCC when compared with placebo the first year after treatment: 1% of patients treated with fluorouracil cream developed cSCC on the face or ears compared with 4% in the placebo group. However, after 4 years of follow-up, this significant difference disappeared, and the incidence of cSCC was 11% in the fluorouracil group vs 12% in the placebo group. In that trial, only veterans with substantial sun exposure and a history of at least 2 keratinocyte carcinomas were included. In other patients with AK, such as those with no history of nonmelanoma skin cancer (NMSC), the risk of developing cSCC is likely lower.

The current study aims to evaluate the risk of invasive cSCC and factors that may contribute to increased risk in patients with multiple AKs. Data on the incidence of invasive cSCC during a 4-year follow-up period were collected in patients who had participated in a randomized clinical trial that compared 4 field-directed treatments of AK. The results of that trial indicated that 1 year after treatment with 5% fluorouracil, the probability of partial (at least 75%) clearance of AK was higher than after treatment with 5% imiquimod cream, methylaminolevulinate photodynamic therapy (PDT), or 0.015% ingenol mebutate gel. The meticulous registration and grading (Olsen grades I-III) of every AK lesion at baseline makes it possible to evaluate the risk of invasive cSCC according to the severity of AK. Moreover, the effect on the risk of other factors, such as allocated treatment, a positive history of NMSC, and need for retreatment, can also be studied.

### Methods

#### Study Design and Study Population

The long-term risk of invasive cSCC was evaluated as a secondary analysis in patients with AK who participated in a single-blinded, multicenter randomized clinical trial with intention to treat that compared the efficacy of 5% fluorouracil cream, 5% imiquimod cream, methylaminolevulinate PDT, and 0.015% ingenol mebutate gel. Patients were recruited from the Department of Dermatology of 4 hospitals in the Netherlands between November 1, 2014, and March 31, 2017. Details on the design and the results from this trial have previously been published, and the trial protocol is available in the trial protocol.

### Findings

In this secondary analysis of a randomized clinical trial of 624 participants that compared 4 field-directed treatments, the 4-year risk of developing SCC in a previously treated area of AK was 3.7%. In patients with severe AK (Olsen grade III), the risk was 20.9%, and the risk was especially high (33.5%) in patients with severe AK who needed additional treatment.

### Treatment Protocol, Randomization, and Outcomes

Patients were randomly assigned to 1 of 4 different treatments in a 1:1:1:1 ratio. Stratifying factors were participating center and severity of AK. Patients were not blinded to the assigned treatment.

A 5% fluorouracil cream was applied by the patient twice daily for 4 weeks. A 5% imiquimod cream was applied by the patient once daily 3 days a week for 4 weeks. Ingelen mebutate 0.015% gel was applied by patients once daily for 3 days. For treatment with methylaminolevulinate PDT, the methylamino-levulinate cream was applied to the treatment area by a trained nurse and covered with light-blocking foil and occlusive dressing for 3 hours. The area was then illuminated with a light-emitting diode for 7.23 minutes. After the PDT session, the treatment site was covered with an occlusive dressing for 24 hours. In case of insufficient response (<75% lesion response) at the first follow-up visit, the treatment strategy allowed for a subsequent treatment with the same allocated treatment.
Risk of Invasive Cutaneous Squamous Cell Carcinoma After Different Treatments for Actinic Keratosis

Table 1. Distribution of Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 624)</th>
<th>Fluorouracil (n = 155)</th>
<th>Imiquimod (n = 156)</th>
<th>Methylaminolevulinate PDT (n = 156)</th>
<th>Ingenol mebutate (n = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>558 (89.4)</td>
<td>136 (87.7)</td>
<td>143 (91.7)</td>
<td>140 (89.7)</td>
<td>139 (88.5)</td>
</tr>
<tr>
<td>Female</td>
<td>66 (10.6)</td>
<td>19 (12.3)</td>
<td>13 (8.3)</td>
<td>16 (10.3)</td>
<td>18 (11.5)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>73 (48-94)</td>
<td>74 (48-90)</td>
<td>73 (59-89)</td>
<td>73 (55-90)</td>
<td>72 (51-94)</td>
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<tr>
<td>History of NMSC</td>
<td>353 (56.6)</td>
<td>90 (58.1)</td>
<td>82 (52.6)</td>
<td>86 (55.1)</td>
<td>95 (60.5)</td>
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<tr>
<td>Target area, median (range), cm²</td>
<td>81 (25-100)</td>
<td>80 (27-100)</td>
<td>86.5 (25-100)</td>
<td>81 (25-100)</td>
<td>78 (25-100)</td>
</tr>
<tr>
<td>No. of AK lesions, median (range)</td>
<td>16 (5-48)</td>
<td>16 (5-48)</td>
<td>16.5 (5-37)</td>
<td>16 (5-38)</td>
<td>15 (5-40)</td>
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<tr>
<td>Severity of AK</td>
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<td></td>
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</tr>
<tr>
<td>Olsen grade I</td>
<td>25 (4.0)</td>
<td>7 (4.5)</td>
<td>7 (4.5)</td>
<td>7 (4.5)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>≥1 Lesion of Olsen grade II</td>
<td>550 (88.1)</td>
<td>137 (88.4)</td>
<td>136 (87.2)</td>
<td>137 (87.8)</td>
<td>140 (89.2)</td>
</tr>
<tr>
<td>≥1 Lesion of Olsen grade III</td>
<td>49 (7.9)</td>
<td>11 (7.1)</td>
<td>13 (8.3)</td>
<td>12 (7.7)</td>
<td>13 (8.3)</td>
</tr>
</tbody>
</table>

In patients who were assigned to 1 of the 3 creams, adherence to the treatment regimen was evaluated using diaries that were completed by patients during treatment. The patients were asked to record the number of times they had applied the cream, the duration of treatment, and reasons for ending the treatment. Moreover, 2 weeks after treatment, patients were contacted by telephone by an investigator (J.P.H.M.K.) who checked how often they had applied the cream.

The primary outcome in this secondary analysis was the 4-year cumulative probability of a histologically proven invasive cSCC in the target area. Secondary outcomes were the associations between risk of developing invasive cSCC and a priori defined potential prognostic factors: type of treatment, the severity of AK lesions, history of NMSC, and additional treatment.

For each patient who had participated in the trial, a study visit was planned for follow-up within a period of 2 to 5 years after the end of treatment. An investigator (S.A.), who was blinded to treatment assignment, evaluated whether a lesion suggestive of cSCC was visible in the treated area using a transparent sheet on which all AK lesions at baseline were drawn. Clinical photographs that were taken at baseline were used as a reference to check the localization of the lesions that were already present at baseline. In case of doubt regarding whether a diagnosed cSCC had arisen at the site of a former AK lesion, an experienced oncodermatologist (K.M., N.W.J.K.-S., A.H.M.M.A., J.P.H.M.K., or M.J.M.d.R.) was consulted as a second observer. If there was any suspicion of malignancy, a punch biopsy was performed. If a patient had been diagnosed with invasive cSCC before the follow-up visit, the exact location and date of diagnosis were retrieved from the electronic patient database of all participating centers. Whether and when patients had received any treatments for AK until the date of the study visit was also registered.

Statistical Analysis
Categorical variables are presented as numbers (percentages) and continuous variables as means (SDs) or medians (ranges). Time-to-event analysis was used to estimate the cumulative probability of invasive cSCC. Follow-up started at the end of treatment. In patients who developed an invasive cSCC, follow-up ended at the date of diagnosis of cSCC. Observations of patients who did not develop a cSCC were censored at the date of the last follow-up visit. Both intention-to-treat and per protocol analyses were performed.

Univariate and multivariate Cox regression models were used to calculate hazard ratios (HRs) with 95% CIs and P values for each a priori defined potential prognostic factor. Additional treatment that occurred later during follow-up was entered as a time-dependent covariate. Fluorouracil was used as the reference group because it was the treatment with the highest effectiveness in terms of AK lesion reduction.

A 2-sided P < .05 was considered statistically significant. All statistical analyses were performed with SPSS Statistics software, version 23 (IBM Corp), and Stata software, version 14.0 (StataCorp LLC).

Results

Patients
A total of 624 patients (558 [89.4%] male and 66 [10.6%] female; median age, 73 years [range, 48-94 years]) were randomized to treatment with fluorouracil (155 patients), imiquimod (156 patients), methylaminolevulinate PDT (156 patients), or ingenol mebutate (157 patients). Relevant baseline characteristics are given in Table 1.

All patients were invited for a follow-up visit between July 1, 2019, and December 31, 2020. The median follow-up was 46 months (IQR, 39-51 months). A total of 74 patients did not attend the follow-up visit mainly because of death from causes unrelated to our study, refusal to attend follow-up visits, inability to visit the hospital, and limited clinical research activities during the COVID-19 pandemic (Figure 1). For these 74 patients, only data for the first 2 years after the end of treatment were available.

During follow-up, 227 patients needed additional treatment with field-directed therapy in the target area if they had
multiple AK lesions. The decision that there was an indication for additional treatment was at the discretion of the treating dermatologist. The probability of an indication for additional treatment within 4 years after the end of the first treatment was lowest after treatment with fluorouracil (23.3%) and significantly increased to 34.5% in the imiquimod group (P = .04), 42.7% in the methylaminolevulinate PDT group (P < .001), and 53.1% in the ingenol mebutate group (P < .001).

Of the 227 patients with an indication for additional treatment, 218 (96.0%) actually received additional treatment. The most frequently prescribed retreatment was fluorouracil; 30 (90.9%) in the fluorouracil group, 36 of 49 patients (73.5%) in the imiquimod group, 61 of 63 patients (96.8%) in the PDT group, and 61 of 73 patients (83.6%) in the ingenol mebutate group received additional treatment with fluorouracil.

**Probability of Invasive cSCC During 4-Year Follow-up**

A histologically proven invasive cSCC in the target area was diagnosed in 26 patients. Of these 26 patients, 4 were in the fluorouracil group, 10 in the imiquimod group, 6 in the methylaminolevulinate PDT group, and 6 in the ingenol mebutate group. All of the invasive cSCCs were observed in patients with Olsen grades II and III AK. Four were located in a preexistent grade III AK lesion, 14 in a preexistent grade II AK lesion, and 3 not in a preexistent AK lesion. For 5 cSCCs, whether they were located in a preexistent AK lesion was uncertain. Seven patients had developed cSCC within 12 months after the end of treatment. In the total study population, the 4-year risk of cSCC after treatment was 3.7% (95% CI, 2.4%-5.7%).

The 1-year and 4-year cumulative risks of developing invasive cSCC within randomized groups are given in the eTable 3 in Supplement 2. The results from the intention-to-treat analysis indicate that the risk of cSCC was lowest in the patient group that was initially treated with fluorouracil (2.2%; 95% CI, 0.7%-6.6%) and was higher in patients treated with imiquimod (5.8%; 95% CI, 2.9%-11.3%), methylaminolevulinate PDT (3.6%; 95% CI, 1.5%-8.6%), or ingenol mebutate (3.0%; 95% CI, 1.1%-7.9%) (Figure 2).

**Risk of Invasive cSCC Associated With Severity of AK and Additional Treatment**

Table 2 details the 4-year cumulative risk of developing invasive cSCC according to severity of AK stratified by additional treatment (no vs yes). The risk of invasive cSCC was higher for patients who had received additional treatment (6.4%; 95% CI, 3.7%-10.7%) compared with patients who did not receive additional treatment (2.1%; 95% CI, 1.0%-4.4%) and was especially increased in patients with Olsen grade III AK who received additional treatment (33.5%; 95% CI, 18.2%-56.3%).

**Table 3** presents the results from multivariate Cox proportional hazards regression analyses. The HRs represent the independent effect of a specific factor after adjustment for the other factors in the model. The relative risk of developing invasive cSCC in patients who received additional treatment was 3.67 (95% CI, 1.52-8.81; P = .004). Olsen grade III AK (vs Olsen grades I-II) was also associated with a significantly higher risk of cSCC (HR, 6.72; 95% CI, 2.94-15.34; P < .001). The adjusted HRs for methylaminolevulinate PDT and ingenol mebutate were close to 1, indicating that after adjustment for other risk factors, the risk of invasive cSCC was comparable with that after fluorouracil treatment. The adjusted HR for imiquimod was 2.09 (95% CI, 0.65-6.74; P = .22).
Discussion

This secondary analysis of a randomized clinical trial evaluated the incidence of invasive cSCC within the specific area that was treated for multiple AK lesions with 1 of 4 field-directed therapies. A histologically proven cSCC in the target area was diagnosed in only 26 patients. The 4-year risk of developing cSCC in a previously treated area of AK was 3.7% overall and varied from 2.2% in patients treated with fluorouracil to 5.8% in patients treated with imiquimod. In patients with severe AK (Olsen grade III), the risk of cSCC was 20.9%, and the risk was especially high (33.5%) in patients with severe AK who needed additional treatment.

The higher risk of SCC development in patients who needed additional treatment, specifically those with 1 or more AK grade III lesions, confirms the findings of previous studies, in which rapid recurrence or persistence after therapy, hyperkeratosis, and palpability were found as risk factors for cSCC in AK. This finding could indicate that the need for additional treatment may be an indicator of an underlying condition that did not respond to treatment.

Whether AKs transform into invasive cSCC or whether sun-damaged skin is the underlying reason why patients with AK also have increased risk of invasive cSCC has long been debated. In the current study, 18 of the 26 invasive cSCCs were located in preexistent lesions. This finding may indicate that AK lesions can transform into invasive cSCC, but the possibility that these lesions were already invasive cSCC before treatment was started cannot be excluded, although clinical assessment of AK was performed by 2 physicians independently. An important question that remains to be answered is whether treatment resulting in reduction of AK lesions also results in preventing progression of those AK lesions into invasive cSCC.

The effectiveness of fluorouracil as a chemoprevention strategy was demonstrated by Weinstock et al, who performed a randomized clinical trial that compared fluorouracil with placebo in veterans with substantial sun exposure and a history of at least 2 keratinocyte carcinomas. After 1 year, the risk of cSCC was significantly lower in the fluorouracil group than in the

![Figure 2. Cumulative Probability of Cutaneous Squamous Cell Carcinoma (cSCC)–Free Survival According to Treatment](https://jamanetwork.com/)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>Fluorouracil (n = 155)</th>
<th>Imiquimod (n = 156)</th>
<th>Methylaminolevulinate PDT (n = 156)</th>
<th>Ingenol mebutate (n = 157)</th>
<th>Total (n = 624)</th>
</tr>
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<tbody>
<tr>
<td>Retreatment</td>
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<td>6</td>
<td>0</td>
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<tr>
<td></td>
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<td>1</td>
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<td>0</td>
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<td></td>
<td>Yes</td>
<td>218</td>
<td>3b</td>
<td>4b</td>
<td>6b</td>
<td>5b</td>
</tr>
<tr>
<td></td>
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<td>2</td>
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<td></td>
<td>Olsen grade III AK</td>
<td>26</td>
<td>2</td>
<td>2</td>
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<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>624</td>
<td>4</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>4-Year risk of cSCC, % (95% CI)</td>
<td>NA</td>
<td>2.2 (0.7-6.6)</td>
<td>5.8 (2.9-11.3)</td>
<td>3.6 (1.5-8.6)</td>
<td>3.0 (1.1-7.9)</td>
<td>3.7 (2.4-5.7)</td>
</tr>
</tbody>
</table>

Abbreviations: AK, actinic keratosis; cSCC, cutaneous squamous cell carcinoma; NA, not applicable; PDT, photodynamic therapy.

* Cutaneous SCC occurred 4 years after treatment.

b Additional treatment was given with fluorouracil.
investigations demonstrate the safety of the product.21 We did not find any evidence of a higher risk of cSCC after ingenol mebutate gel treatment compared with the other treatments.

The current randomized clinical trial allowed for comparison of long-term SCC risk after 4 different field-directed treatments. The HRs using the fluorouracil group as the reference category show a slightly increased risk of cSCC in patients who initially had one of the other treatments. However, none of these HRs were statistically significant, and approximately one-third of patients received additional treatment, mostly with fluorouracil. Therefore, the findings in this study do not permit definite conclusions on whether fluorouracil is the most effective treatment for preventing the development of invasive SCC.

The finding that imiquimod treatment was associated with an increased risk of cSCC may be attributable to chance. Currently, no studies have found that imiquimod treatment of AK leads to an increased risk of developing cSCC. An alternative explanation may be that in the imiquimod group, only 25% of patients received additional treatment with fluorouracil, whereas in the methylaminolevulinate PDT and ingenol mebutate groups, these percentages were much higher.

Ingenol mebutate has been reported to potentially be linked to increased risk of developing skin cancer.23,24 Consequently, the European Medicines Agency has recommended that the use of ingenol mebutate be suspended until further investigations demonstrate the safety of the product.21 We did not find any evidence of a higher risk of cSCC after ingenol mebutate gel treatment compared with the other treatments.

Limitations
This study has some limitations. The sample size was calculated to compare 4 field-directed treatments of AK with respect to effectiveness on the reduction of AK lesions and not for comparing long-term risk of invasive cSCC. Thus, a limitation is the small number of cSCC events, resulting in low power to detect small but relevant differences in long-term risk of cSCC with significance. Furthermore, the decision to give additional treatment was at the discretion of the treating dermatologist, and there were no predefined criteria for the need for additional treatment. However, misclassification of the need for additional treatment by dermatologists can occur in 2 directions: no additional treatment in patients needing additional treatment and additional treatment in patients not needing additional treatment. Such so-called nondifferential misclassification generally leads to bias of a true effect toward the null value. Therefore, it is likely that the positive association that was found in this study represents a real effect that has been underestimated rather than overestimated.23

Finally, a placebo group was not available: all patients received treatment with an active ingredient. Therefore, more studies are necessary to conclude whether treatment could be omitted in patients with low-risk AK.

Conclusions
In this secondary analysis of a randomized clinical trial, the risk of invasive cSCC was highest in patients with Olsen grade III AK lesions and was substantially increased in patients who received additional treatment. We therefore recommend close follow-up of these patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
<th>Cumulative risk of cSCC, % (95% CI)</th>
<th>Univariate analysis, HR (95% CI)</th>
<th>P value</th>
<th>Multivariate analysis, HR (95% CI)</th>
<th>P value</th>
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<td>History of NMSC</td>
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<tr>
<td>Yes</td>
<td>353</td>
<td>4.8 (2.9-7.8)</td>
<td>1.21 (0.53-2.74)</td>
<td>.65</td>
<td>1.39 (0.60-3.19)</td>
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<tr>
<td>Olsen grade III&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49</td>
<td>20.9 (10.8-38.1)</td>
<td>7.11 (1.16-15.99)</td>
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<td>.54</td>
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<td>.65</td>
<td>0.86 (0.24-3.13)</td>
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</tbody>
</table>

Abbreviations: AK, actinic keratosis; cSCC, cutaneous squamous cell carcinoma; HR, hazard ratio; NA, not applicable; NMSC, nonmelanoma skin cancer; PDT, photodynamic therapy.

<sup>a</sup> One or more lesions of Olsen grade III.

<sup>b</sup> No cSCCs were found in patients with Olsen grade I.
RISK OF INVASIVE CUTANEOUS SQUAMOUS CELL CARCINOMA AFTER DIFFERENT TREATMENTS FOR ACTINIC KERATOSIS

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AUTHOR CONTRIBUTIONS

Dr Ahmady had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Ahmady, Jansen, Nelemans. Acquisition, analysis, or interpretation of data: Ahmady, Jansen, Nelemans, Arits, de Rooij, Kessels, Quaedvlieg. Drafting of the manuscript: Ahmady, Jansen, Nelemans. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Ahmady, Jansen, Nelemans. Obtained funding: Essers, Kessels-Smeets, Mosterd. Administrative, technical, or material support: Jansen, Kessels, Mosterd. Supervision: Nelemans, Kessels, Arits, de Rooij, Essers, Quaedvlieg, Kessels-Smeets, Mosterd.

CONFLICT OF INTEREST DISCLOSURES: Dr Jansen reported receiving grants from the Netherlands Organization for Health Research and Development (ZonMW) during the conduct of the study. Dr Arits reported receiving grants from ZonMW during the conduct of the study. Dr Kessels-Smeets reported receiving grants from ZonMW during the conduct of the study. Dr Mosterd reported receiving grants from government during the conduct of the study and speaker fees from Leopharma, Galderma, Novartis, and Sun Pharma outside the submitted work. No other disclosures were reported.

FUNDING/SUPPORT: This study was supported by grant BO-83600-98-3054 from the ZonMW.

ROLE OF THE FUNDER/SPONSOR: The funding source had a role in the conduct of the study but no role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

DATA SHARING STATEMENT: See Supplement 3.

ADDITIONAL CONTRIBUTIONS: We thank the patients who participated in this study and all nurse practitioners and employees of the administrative departments of the participating hospitals.

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