

# Immunomodulators for Non-Melanoma Skin Cancers: Updated Perspectives

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**Abstract:** Non-melanoma skin cancers (NMSCs) are the most common cancers worldwide and may be associated with significant morbidity and mortality, especially in immunosuppressed populations. Successful management of NMSC must take primary, secondary and tertiary prevention strategies into consideration. In response to an improved understanding of the pathophysiology of NMSC and associated risk factors, multiple systemic and topical immunomodulatory drugs have been developed and integrated into clinical practice. Many of these drugs are efficacious in the prevention and treatment of precursor lesions (actinic keratoses; AKs), low-risk NMSC, and advanced disease. The identification of patients at high risk for the development of NMSC is critical in reducing disease morbidity. Understanding the various treatment options available and their comparative effectiveness is paramount for developing a personalized treatment regimen for such patients. This review article provides an updated overview of the various topical and systemic immunomodulatory drugs available for the prevention and treatment of NMSC, and the published data supporting their use in clinical practice.

**Keywords:** non-melanoma skin cancer, squamous cell carcinoma, basal cell carcinoma, keratinocyte carcinoma

## Introduction

Non-melanoma skin cancers (NMSCs) are the most common cancers worldwide. In the United States (US), the incidence of basal cell carcinoma (BCC) is greater than 2 times that of cutaneous squamous cell carcinoma (cSCC), exceeding the incidence of all other malignancies combined.<sup>1</sup> The primary risk factor contributing to the development of NMSC development is chronic exposure to ultraviolet (UV) radiation. UV light leads to direct deoxyribonucleic acid (DNA) damage, free radical production, and cutaneous immunosuppression by way of modifying and suppressing the localized innate and adaptive cytokine profile and cellular surveillance.<sup>2</sup> Other risk factors including advanced age, Fitzpatrick skin type I–II, history of ionizing radiation, certain genetic diseases and systemic immunosuppression may also contribute to the development of NMSC. Among the immunosuppressed, the subsets of populations most vulnerable to the development of NMSC include solid organ transplant recipients (SOTRs), patients with hematologic malignancies, and those with other immunosuppressive conditions such as human immunodeficiency virus (HIV). The risk of developing cSCC and BCC in the SOTR population is estimated to be 40–250 and 5–10 times higher than the general population, respectively.<sup>3,4</sup> Patients with chronic lymphocytic leukemia (CLL) are 1.86–8.6 times more likely to develop cSCC than the general population.<sup>5</sup> The risk of cSCC metastasis in the general population is approximately 4%, but among SOTRs and certain immunosuppressed individuals, the risk may be 2–3 times greater.<sup>6,7</sup> In fact, metastatic skin cancer is one of the leading causes of mortality in SOTRs.<sup>8</sup> Given the significant morbidity and mortality associated with NMSC in at-risk populations, multi-faceted prevention and treatment approaches are critical.

Destructive and surgical approaches are generally the first-line treatment options for low-risk cSCC and BCC. These include cryosurgery, electrodesiccation and curettage, and standard surgical excision. Complete margin analysis surgery, such as Mohs micrographic surgery, is generally reserved and preferred for high-risk cSCC and BCC. Treatment

selection depends on host risk factors, clinical and histologic features, and anatomic location of the malignancy. Advanced or metastatic disease may not be amenable to surgical and/or destructive therapies, and systemic therapy may be necessary. Aside from the many treatment options for confirmed disease, primary and secondary prevention strategies aimed at reducing overall disease burden are similarly important. This review article will discuss in detail the various immunomodulatory treatment options and the current evidence supporting their use in both the prevention and treatment of NMSC. The safety and efficacy of systemic and topical retinoids, nicotinamide, capecitabine, systemic and topical non-steroidal anti-inflammatories (NSAIDs), mammalian target of rapamycin (mTOR) inhibitors, checkpoint inhibitors, topical 5-fluorouracil (5-FU), topical imiquimod (IMI), topical ingenol mebutate (IMB), and photodynamic therapy (PDT) will be discussed in detail.

## Systemic Immunomodulators

### Oral Retinoids

Retinoids are natural or synthetic small molecule hormones that mimic the biologic activity of vitamin A, activating nuclear receptors and regulating gene transcription. This ultimately affects the expression of proteins involved in cell growth and regulation.<sup>3,9</sup> In addition to their anti-inflammatory and anti-proliferative effects, retinoids have demonstrated immunomodulatory and anti-inflammatory benefits by way of stimulating T cell mediated cytotoxic effects, inhibiting the accumulation of leukocytes in the stratum corneum and inhibiting blastogenesis of lymphocytes.<sup>10</sup> Cells infected with human papillomavirus are 10–100 times more sensitive to retinoic acid growth inhibition than uninfected keratinocytes, which may serve as an explanation for the modulation of NMSC development, particularly cSCC.<sup>11,12</sup> Retinoids have been studied most extensively in the SOTR population as chemoprophylaxis against keratinocyte carcinomas, but they may also be useful in other high-risk populations.

A double-blind, randomized controlled trial (RCT) published in 1995 by Bavinck et al demonstrated that the administration of acitretin to renal transplant patients at a dose of 30 mg/day for 6 months resulted in a 36% risk reduction in the development of cSCC when compared to placebo.<sup>13</sup> A more recent 2002 open-label, randomized crossover trial of renal transplant patients receiving between 25 and 50 mg/day of acitretin demonstrated a statistically significant reduction in cSCC incidence compared to those in the drug-free interval.<sup>14</sup> Patients evaluated in this study had either >3 cSCCs or BCCs within the previous 5 years or  $\geq 10$  or more AKs. Thirty-nine percent of patients withdrew due to side effects including rash, nausea, headache, epistaxis, and elevated serum cholesterol levels.

Many other case series and retrospective studies have reproduced a significant risk reduction in the development of cSCC with the administration of systemic retinoids. A recent systematic literature review published in 2021 by Badri et al reported an overall 54% risk reduction in the annual development of cSCC and a 73% risk reduction in the development of BCC across relevant studies examining the use of acitretin for chemoprophylaxis in renal transplant recipients.<sup>15</sup> Some studies report a higher efficacy of acitretin in the prevention of cSCC compared to BCC,<sup>14</sup> however a recent RCT investigating 70 non-SOTRs receiving acitretin 25 mg orally 5 days per week suggested a similar efficacy in the prevention of both NMSCs.<sup>16</sup>

Acitretin is preferred over etretinate, which is no longer available for use in the US due to associated toxicities. Isotretinoin may have some chemopreventive benefit in NMSC, although results from studies are conflicting. A 3-year controlled, prospective study from 1988 demonstrated a statistically significant 63% reduction in skin cancer incidence in patients with xeroderma pigmentosum treated with a high dose (2 mg/kg/day) of isotretinoin compared to a two-year drug-free interval prior to the intervention.<sup>17</sup> Protective effects waned within 3 months after treatment withdrawal. One case report from 1996 showed a 50% reduction in NMSC within 2 months with the use of isotretinoin 0.5–1 mg/kg per day in a renal transplant patient,<sup>18</sup> however RCTs have failed to show consistent reproducible results.<sup>19</sup> Notably, an RCT of 525 patients with  $\geq 4$  cSCCs or BCCs did not show any statistically significant correlation between 5 and 10 mg/day of isotretinoin or 25,000 units/day of retinol administration and NMSC incidence, though it has been suggested that the low doses administered in this study may have contributed to the lack of effectiveness.<sup>20</sup>

The current 2022 version of the National Comprehensive Cancer Network (NCCN) guidelines for the management of cSCC notes that acitretin and isotretinoin have proven effective in the prevention of both AKs and cSCC in high-risk

patients. The guidelines for the management of BCC also note that acitretin might be effective for prevention in high-risk patients.<sup>16,21</sup> (Table 1) Common side effects of oral retinoids including hepatotoxicity, teratogenicity, xerosis cutis, and lipid abnormalities may limit clinical use, and therapeutic effects have been shown to diminish within months after discontinuation. Although there are few specific guidelines regarding patient selection and dosing regimens, some experts consider starting oral retinoids in patients who develop  $\geq 5$  cSCC of any stage over 2–3 years, 1 Brigham and Women's Hospital (BWH) T2b/T3 cSCC in the setting of diffuse UV damage, or field cancerization responding sub-optimally to PDT or 5-FU.<sup>22</sup> The NCCN guidelines for the management of BCC are less specific, however do suggest that individuals at high risk of developing NMSC may benefit from acitretin administration.<sup>21</sup>

## Nicotinamide

Nicotinamide is a water-soluble amide form of niacin (vitamin B3) and is essential in the production of ATP by way of nicotinamide adenine dinucleotide. Nicotinamide prevents UV radiation induced cellular ATP depletion and reduces UV associated suppression of antitumor immunity, thereby counteracting UV-induced carcinogenesis and the development of NMSC.<sup>23–26</sup> Nicotinamide has shown potent *in vitro* immunomodulatory effects by inhibiting proinflammatory cytokines including interleukins 6, 8, 1 $\beta$ , and tumor necrosis factor  $\alpha$ .<sup>27</sup> Although the mechanisms are not fully understood, it is thought that nicotinamide exerts a chemoprotective benefit and reduces the immunosuppressive effect of sunlight by modulating DNA repair, regulating apoptosis, and up-regulating immune function-related genes that are typically down-regulated by UV irradiation.<sup>28,29</sup>

A recent Phase 3 double-blind, randomized, placebo-controlled trial published in 2015 demonstrated a 23% relative rate reduction in the development of new NMSCs when study participants were administered 500 mg of nicotinamide twice daily over a 12-month period when compared to placebo.<sup>24</sup> Participants selected for this study were immunocompetent individuals 18 years of age or older, with  $\geq 2$  histologically confirmed NMSCs in the previous 5 years. Of note, this effect was not maintained by 6 months after drug discontinuation. The study also demonstrated a statistically significant reduction in the development of new AKs (11%), which plateaued after 9 months of treatment, consistent with findings in prior studies. A Phase 2 RCT investigating nicotinamide for chemoprophylaxis in 22 renal transplant recipients with  $\geq 2$  histologically confirmed NMSCs in the previous 12 months showed a 35% relative difference in the rate of NMSC and 16% reduction in AKs. These results were not statistically significant, possibly owing to a small sample size. Further trials investigating the utility of nicotinamide in SOTRs are underway.<sup>25,30</sup>

Nicotinamide is generally well tolerated with few side effects at the recommended dosage; however, the therapeutic effects have been shown to wane shortly following cessation. The current NCCN guidelines for the management of cSCC do not give clear specifications on the selection of patients and use of nicotinamide, but there is mention that it may be effective in reducing the development of cSCC.<sup>1</sup> Some experts currently recommend nicotinamide to patients who have had  $>1$  cSCC or who display field cancerization.<sup>22</sup> The NCCN guidelines for the management of BCC suggest that the use of nicotinamide may be effective, citing data from Chen et al<sup>21,24,25</sup> (Table 1) Although the benefits appear to be positive, long-term data is needed to characterize the utility of nicotinamide more fully in at-risk populations.

## Capecitabine

Capecitabine is a prodrug of 5'-deoxy-5-fluorouridine, which is ultimately converted to its active metabolite 5-FU by the liver, which subsequently inhibits thymidylate synthase.<sup>31</sup> Capecitabine has been shown to selectively reduce inflammatory cytokines, while simultaneously increasing anti-inflammatory cytokines. It has also been hypothesized that fluorouracil, a metabolite of 5-FU, depletes myeloid-derived suppressor cells, which accumulate during the progression of a malignancy and suppress activation of T cells.<sup>32</sup>

Capecitabine has shown efficacy in the treatment of advanced cSCC in non-SOTRs when used in combination with subcutaneous interferon alpha.<sup>33</sup> The drug is most commonly used in its currently approved indications for the treatment of breast and colon malignancies. In patients previously treated with capecitabine for various solid tumor malignancies, inflammation, followed by resolution of AKs occurred incidentally, leading to studies investigating its efficacy in the treatment and prevention of NMSC.<sup>34,35</sup>

**Table 1** Immunomodulatory Drug Regulations, FDA Approvals, and Mechanism of Action for Treatment of NMSC

	<b>cSCC NCCN Guidelines</b>	<b>BCC NCCN Guidelines</b>	<b>AK NCCN Guidelines</b>	<b>cSCC FDA Indications</b>	<b>BCC FDA Indications</b>	<b>AK FDA Indications</b>	<b>Immunomodulatory Mechanism of Action</b>
<b>Systemic Retinoids</b>	Effective in reduction of cSCC in high-risk patients	Might be effective for prevention in high-risk individuals	Effective in reducing the development of AKs in some high-risk patients, though therapeutic effects are not observed long-term (Level 2A - uniform consensus based on lower level evidence), side effects may be significant, and caution is advised when treating women of childbearing age	Not FDA approved	Not FDA approved	Not FDA approved	Inhibit accumulation of leukocytes in the stratum corneum and blastogenesis of lymphocytes via stimulation of T cell mediated cytotoxic effects <sup>10</sup>
<b>Nicotinamide</b>	May be effective in reducing the development of cSCC, further research needed for long-term clinical benefits	Use of nicotinamide may be effective in reducing the development of BCCs	Further clinical research needed to determine if long-term clinical benefit exists for patients at risk of developing multiple AK lesions	Not FDA approved	Not FDA approved	Not FDA approved	Inhibit proinflammatory cytokines including interleukins 6, 8, 1 $\beta$ , and tumor necrosis factor $\alpha$ . <sup>27</sup>
<b>Capecitabine</b>	Useful for treatment of patients who are ineligible for or have progressed on checkpoint inhibitors and clinical trials, or when surgery is impractical due to high cSCC burden	May be effective for the prevention of BCC in high-risk individuals	No recommendation	Not FDA approved	Not FDA approved	Not FDA approved	Selectively reduces some anti-inflammatory cytokines and increases others, depletes myeloid-derived suppressor cells that accumulate during malignancy and suppress activation of T cells <sup>32</sup>
<b>Systemic NSAIDs</b>	No recommendation	Celecoxib may be effective for the prevention of BCC in high-risk individuals	No recommendation	Not FDA approved	Not FDA approved	Not FDA approved	Enhance anti-tumor immunity, augment T cell cytotoxicity and improve cancer immunosurveillance <sup>42</sup>

<b>mTOR Inhibitors</b>	Incorporation of mTOR inhibitors in OTRs undergoing immunosuppressive therapy may be considered in cases of life-threatening cancer or rapid development of multiple tumors	No recommendation	No recommendation	Not FDA approved	Not FDA approved	Not FDA approved	Inhibit the serine/threonine kinase protein, mTOR, to prevent downstream signaling pathways for lymphocyte proliferation and antibody production <sup>167</sup>
<b>Checkpoint Inhibitors</b>	Cemiplimab or pembrolizumab preferred for locally advanced, recurrent, or metastatic disease when curative RT or surgery is not feasible	Cemiplimab may be considered for the treatment of distant metastases and is recommended for the treatment of locally advanced or metastatic BCC previously treated with an HHI or for whom an HHI is not appropriate	No recommendation	Approved for cSCC that has spread or recurred or cannot be treated with surgery or radiation therapy <sup>168</sup>	Approved for treatment of BCC that cannot be removed by surgery or has spread after treatment with HHI therapy or if HHI therapy cannot be used <sup>168</sup>	Not FDA approved	Inhibit immune checkpoint target proteins, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 receptor (PD-1) and ligand (PD-L1), activating T cells to target tumor cells, leading to tumor destruction
<b>Topical Retinoids</b>	Not recommended for prophylactic use in patients at high risk for cSCC	Tazarotene may be effective for the prevention of BCC in high-risk individuals	Not recommended for prophylactic use in patients at high risk for multiple AKs, acceptable form of pre-treatment for hyperkeratotic AKs prior to treatment with other modalities	Not FDA approved	Not FDA approved	Not FDA approved	Normalize hyperkeratinization, altering the skin microenvironment via regulation of inflammatory mediators and toll-like receptors, and inhibit chemotaxis of polymorphonuclear cells <sup>92</sup>
<b>Topical 5-FU</b>	Therapy should be reserved for patients with SCCIS, can be considered in anatomically challenging locations	May be considered for the treatment of superficial BCC though cure rates may be lower than with surgical treatment modalities	Preferred with or without calcipotriene over other topical therapies for the treatment of AKs	Not FDA approved	FDA approved to treat BCC that is superficial and in patients whose tumors cannot be treated with conventional therapy <sup>169</sup>	FDA approved	Increases immunity of CD4+ T cells against AKs when combined with calcipotriol <sup>103</sup>

(Continued)

Table 1 (Continued).

	<b>cSCC NCCN Guidelines</b>	<b>BCC NCCN Guidelines</b>	<b>AK NCCN Guidelines</b>	<b>cSCC FDA Indications</b>	<b>BCC FDA Indications</b>	<b>AK FDA Indications</b>	<b>Immunomodulatory Mechanism of Action</b>
<b>Topical Imiquimod</b>	Consideration of use is appropriate for SCCIS, especially in anatomically challenging locations	May be considered for the treatment of superficial BCC though cure rates may be lower than with surgical treatment modalities	Accepted treatment for AKs	Not FDA approved	Approved for treatment of superficial BCC in immunocompetent adults	Approved for treatment of AKs in immunocompetent adults <sup>170</sup>	Activates toll-like receptors, regulating mRNA expression of genes responsible for producing cytokines by monocytes, macrophages, and epidermal keratinocytes to enhance innate and cell-mediated immune response against tumor activity and induce pro-apoptotic pathways <sup>117</sup>
<b>Topical Ingenol Mebutate</b>	Removed from most recent guidelines	No recommendation	Removed from most recent guidelines	Not FDA approved	Not FDA approved	Not FDA approved	Agonist for intracellular protein kinase C, which induces rapid cellular necrosis and a neutrophil-mediated form of antibody-dependent cellular cytotoxicity <sup>171</sup>
<b>Topical NSAIDs</b>	No recommendation	No recommendation	Category 2B consideration (appropriate based on lower-level evidence)	Not FDA approved	Not FDA approved	Not FDA approved	Enhances anti-tumor immunity, augments T cell cytotoxicity and improves cancer immunosurveillance <sup>42</sup>
<b>Photodynamic Therapy</b>	Accepted treatment modality for SCCIS though cure rates may be lower than with surgical treatment modalities	May be considered for the treatment of superficial BCC though cure rates may be lower than with surgical treatment modalities	Accepted for the treatment of AKs	Not FDA approved	Not FDA approved	ALA-PDT and MAL-PDT are FDA approved <sup>172</sup>	Application of a photosensitizing agent followed by irradiation of light generates reactive oxygen species (ROS) which leads to cell death, augments host immune response by recruiting immune cells to the treated area <sup>149,150</sup>

A retrospective, case-observational study published in 2010 investigating the efficacy of oral low dose capecitabine as chemoprophylaxis in 15 SOTRs showed significant reduction in both pre-cancerous lesions and NMSCs. In this study, 1 gm/m<sup>2</sup>/day of capecitabine was administered to patients with  $\geq 2$  NMSCs within the prior 6 months or  $\geq 10$  new AKs requiring treatment within 12 months. The drug was given in two daily doses on days 1–14 of a 21-day cycle, resulting in an individual incidence reduction of cSCC ranging from 56% to 100%. Over half of the participants enrolled in the study also had reductions in AK incidence, and 40% showed a reduction in BCCs, although the pre-intervention incidence was low. One-third of participants discontinued treatment by 1 year, and side effects including fatigue, hand-foot syndrome and diarrhea were common.<sup>36</sup>

A recent case series published in 2013 by Endrizzi et al reviewed outcomes of systemic capecitabine administration in 10 SOTRs. In this series, patients with high rates of new NMSC were administered a starting dose of 500 to 1500 mg/m<sup>2</sup>/day (based on body size and renal function) on days 1 and 14 of a 21-day cycle. Over a period of 12 months of treatment, a statistically significant reduction in the rate of cSCC was observed, with a range of 43–100%. A decrease in the number of clinically observable AKs was seen in 9 of 10 patients. There were too few BCCs to draw conclusions about the potential chemoprophylactic effects of capecitabine in this NMSC type.<sup>37</sup>

Capecitabine may be a useful alternative for reducing the overall burden of AKs and cSCC in the appropriate patient population when other treatments have failed despite optimization. Treatment may be limited by side effects including palmoplantar erythrodysesthesia, which may occur in up to 71% of patients, as well as acral erythema, stomatitis, pyogenic granulomas, hyperpigmentation and hand-foot syndrome.<sup>31,38</sup> In the case series by Endrizzi et al, 7 of 10 study participants required dose adjustments, and 2 discontinued treatment as a result of adverse effects (AEs). Use may be limited by renal insufficiency as well as the rare presence of dihydropyrimidine dehydrogenase deficiency, which may cause severe toxicity and death.<sup>31,39</sup>

Currently, there are no guidelines or recommendations for the use of capecitabine as chemoprophylaxis or treatment of NMSC. The NCCN guidelines for the management of cSCC do suggest that capecitabine may be considered in SOTRs when surgery is impractical due to high tumor burden.<sup>1,37</sup> (Table 1) The guidelines for the management of BCC are less specific, although consideration of capecitabine for individuals at high risk for developing NMSC is noted.<sup>21</sup> Generally, initiation of capecitabine should be pursued in consultation with medical oncology as intensive monitoring is necessary.

## Non-Steroidal Anti-Inflammatory Drugs

NSAIDs decrease prostaglandin synthesis by way of cyclooxygenase-2 (COX-2) inhibition, and overexpression of COX-2 has been suggested to play a role in the pathogenesis of NMSC.<sup>40</sup> COX-2 levels increase within the epidermis after UV exposure, and the enzyme has been detected in AKs, cSCCs, and BCCs.<sup>41</sup> NSAIDs have gained considerable interest for their immunomodulatory action in the prevention and treatment of various cancers.<sup>42</sup> Although not entirely understood, there is evidence supporting the enhancement of anti-tumor immunity, augmentation of T cell cytotoxicity and improvement in cancer immunosurveillance.<sup>42</sup> This insight has led to studies investigating the efficacy of both topical and systemic NSAIDs in the treatment of NMSC. To date, there have been conflicting results of studies evaluating the use of systemic NSAIDs for this indication.

A double-blind RCT trial published in 2010 by Elmetts et al showed a statistically significant reduction in NMSC in patients administered 200 mg/day of celecoxib when compared to placebo after 11 months of treatment (mean cumulative tumor number per patient 0.14 vs 0.35, respectively). Patients enrolled in this study had 10–40 AKs and  $\geq 1$  previous histologically confirmed AK and/or NMSC.<sup>43</sup> Interestingly, although celecoxib was effective in reducing the incidence of cSCC, the same effect was not seen with AKs.

Although these data are promising, other studies have failed to show a reproducible correlation between NSAIDs and cSCC risk. A retrospective case-control study of 415 patients published in 2010 by Asgari et al did not show any negative correlation between NSAID use and cSCC risk, and a meta-analysis published in 2014 also failed to show any statistically significant protective effect of NSAIDs on NMSC incidence.<sup>44</sup>

The most recent meta-analysis published in 2015 by Muranushi et al included 2 other studies that were not investigated in the prior meta-analysis by Zhang et al. This meta-analysis included 3 cohort studies and 3 case-control studies for the use of aspirin, and 7 studies (1 RCT, 3 cohort and 3 case control) investigating the use of non-aspirin

NSAIDs in the prevention of NMSC.<sup>43,45–52</sup> The data from this analysis showed a statistically significant reduction in cSCC risk by 15 and 18% with the use of non-aspirin NSAIDs or any NSAIDs, respectively.<sup>53</sup>

Although there may be some benefit in the use of systemic NSAIDs, this must be weighed with the risk of side effects and other AEs. The use of COX-2 inhibitors has fallen out of favor due to the increased risk of adverse cardiovascular effects, in addition to other side effects including bleeding risk and adverse gastrointestinal effects.<sup>54</sup> Given mixed results, risk for side effects, and availability of other efficacious options, the use of NSAIDs in the chemoprevention of NMSC is currently limited.

## mTOR Inhibitors

SOTRs have a risk for NMSC that is well beyond that of other immunosuppressed cohorts, estimated to be up to 10 times greater than HIV positive individuals. This suggests that both the mechanism and level of immunosuppression play a role in the risk of NMSC development and overall tumor burden.<sup>8</sup> Studies investigating the relationship between immunosuppressive regimens and the risk of NMSC development in SOTRs have shown variability of the impact of exogenous immunosuppression versus various immunosuppressive conditions (eg HIV, CLL, autoimmune disease, etc.) on overall risk.

Calcineurin inhibitors (cyclosporine and tacrolimus) have historically been a cornerstone of post-transplant immunosuppressive regimens, and although they are efficacious in preventing organ rejection, they are known to enhance tumor development and increase risk for cutaneous malignancies. In contrast, mTOR inhibitors reduce the proliferation and growth of tumors, and have been shown to reduce the risk of NMSC development in SOTRs.<sup>55</sup>

A recent 9-year retrospective cohort study from 2016 evaluated 329 recipients of various organ transplants and showed an 11.6% reduction in skin cancer risk in SOTRs who were treated with sirolimus following the diagnosis of a posttransplant cancer compared to those not treated with sirolimus.<sup>56</sup> A phase 3, multicenter, randomized, open-label trial from 2012 compared the incidence of cSCC in patients taking calcineurin inhibitors compared to those who were transitioned from calcineurin inhibitors to sirolimus. The results demonstrated a cSCC-free survival that was significantly longer in patients taking sirolimus, and a relative risk of 0.56.<sup>57</sup> Most of the patients receiving sirolimus experienced an AE, most commonly edema, acneiform eruptions, and aphthous ulcers. The most common serious AEs reported were pneumonitis and diarrhea.<sup>57</sup>

A prospective, multicenter, open-label RCT from 2012 enrolled 86 renal transplant recipients on calcineurin inhibitor based immunosuppressive regimens for at least 1 year and randomized half of the group to convert their calcineurin inhibitor to sirolimus. The data showed a significantly lower yearly NMSC rate among those taking sirolimus compared to those who remained on calcineurin inhibitors (1.31 vs 2.48 lesions/patient-year, respectively). In the sirolimus group, higher rates of acne, diarrhea, epistaxis, oral ulcers, edema, rash, pneumonitis, and albuminuria were noted. 42.6% of participants discontinued sirolimus due to side effects, most commonly pneumonitis, and diarrhea.<sup>58</sup> Notably, no participants in the sirolimus arm experienced rejection of their transplanted kidney, suggesting adequate immunosuppression.

Despite one recent 2016 retrospective cohort study that failed to demonstrate a reduction in cSCC risk with prior sirolimus exposure,<sup>59</sup> there are multiple other studies that have reproduced positive results without an increased risk for organ rejection.<sup>60–65</sup> Other side effects of sirolimus that may limit its use include cytopenias, lymphedema, mucositis, interstitial lung disease, metabolic syndrome, gastrointestinal side effects, renal toxicity, and thromboembolic disease. Wound healing complications have also been observed with the use of mTOR inhibitors,<sup>66</sup> and special consideration must be made to reduce the risk of post-operative complications, especially in patients with other risk factors for poor wound healing.<sup>67</sup>

Currently, the NCCN guidelines version 2.2022 for the management of cSCC note that consideration should be given to either reduce the level of immunosuppression and/or incorporate mTOR inhibitors into the immunosuppressive regimen of SOTRs in cases of life-threatening skin cancer, or the rapid development of multiple tumors. (Table 1) Expert consensus suggests that revision of immunosuppression should also be considered in SOTRs at risk for significant disease burden or poor outcomes from cSCC.<sup>68</sup> The guidelines for the management of BCC do not comment on revision of immunosuppressive regimens for the purpose of BCC prevention.

## Checkpoint Inhibitors/Immunotherapy

Checkpoint inhibitors generate an antitumor response by blocking immune checkpoint target proteins cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 receptor and ligand (PD-1 and PD-L1, respectively). This ultimately activates T cells to target tumor cells, leading to tumor destruction. The development of systemic immunotherapy has revolutionized the treatment of multiple different skin cancers, including Merkel cell carcinoma, melanoma, and locally advanced and metastatic NMSC.<sup>69,70</sup> There are currently five immune checkpoint inhibitors approved for use in cutaneous malignancies: nivolumab, pembrolizumab, cemiplimab, avelumab, and ipilimumab.

Cemiplimab, an IgG4 monoclonal antibody that inhibits PD-1, was approved by the US Food and Drug Administration (FDA) in 2018 for the treatment of metastatic or locally advanced cSCC in patients who were not candidates for curative surgery or RT. Results published in 2020 from the EMPOWER-CSCC 1 trial, an open-label, phase 2, single-arm study evaluating the safety and efficacy of cemiplimab in 78 patients with locally advanced cSCC who were not candidates for surgery or RT, report an objective response in 44% of patients with complete response (CR) in 13% and partial response (PR) in 31% among patients treated with cemiplimab 3 mg/kg IV every 2 weeks for up to 96 weeks. Forty-four percent of patients experienced grade 3 or 4 AEs, most commonly hypertension and pneumonia.<sup>71</sup> Two patients had treatment-emergent AE that resulted in death, one of which was attributable to the study drug.<sup>71</sup> A more recent phase 2, confirmatory, multicenter, nonrandomized study evaluated the efficacy of neoadjuvant cemiplimab in patients with resectable Stage II–IV (M0) cSCC.<sup>72</sup> Seventy-nine patients received 350 mg of IV cemiplimab every 3 weeks for 4 doses prior to surgical resection. The ORR was 68.4%, with a pathological CR of 50.6% and a major pathologic response in an additional 12.7%.<sup>72</sup> 17.7% of patients developed AEs that were at least grade 3 in severity, and the most commonly reported AEs were rash, fatigue, nausea and diarrhea.<sup>72,73</sup> Four AEs were observed that resulted in death, one of which was possibly related to treatment.<sup>72</sup> Durability of response is currently under investigation, showing continued response rates at 3 year follow-up.<sup>74</sup>

Cemiplimab is currently also FDA approved for the treatment of locally advanced or metastatic BCC previously treated with a hedgehog inhibitor (HHI), or when HHIs are contraindicated.<sup>75–78</sup> A open-label, multicenter, single-arm, phase 2 trial evaluated the efficacy of cemiplimab in 84 patients with locally advanced or metastatic BCC who were intolerant to HHIs or who had progressive disease despite HHI therapy.<sup>76</sup> Patients received 350mg of IV cemiplimab every 3 weeks for a maximum of 93 weeks. Six percent of patients demonstrated a CR to therapy and 25% demonstrated a PR after a median follow-up duration of 15 months. There were various adverse events reported, and the most common serious AEs that were considered treatment related were adrenal insufficiency and colitis.<sup>76</sup> Three treatment-emergent deaths were reported, none of which were attributed to the study drug.<sup>76</sup>

Pembrolizumab, another PD-1 inhibitor, was approved by the FDA for the treatment of recurrent and metastatic cSCC in June of 2020.<sup>79</sup> The KEYNOTE-629 Phase II trial is an ongoing multicenter, nonrandomized, single-arm, open-label trial investigating subjects with histologically confirmed locally advanced, recurrent, and metastatic cSCC who are not eligible for surgical resection, or not cured by surgery or RT. In the second interim analysis published in October 2021, a 50.0% ORR with 16.7% CR and 33.3% PR was reported among a cohort of subjects with locally advanced disease receiving pembrolizumab 200 mg IV every 3 weeks for up to 24 months. The recurrent/metastatic cohort showed a 35.2% ORR with 10.5% CR and 24.8% PR, and an estimated response durability of 77.8% at  $\geq 12$  months.<sup>80–82</sup>

CARSKIN, an open-label, uncontrolled, multicenter phase 2 trial also examined the effects of pembrolizumab in subjects with unresectable cSCC. Data showed a statistically significant ORR of 41% at 15 weeks, including 13 PRs and 3 CRs. AEs occurred in 71% of subjects, and 7% were  $\geq$  grade 3 adverse reactions, including diarrhea, colitis, vasculitis, secondary de novo head and neck cancer, cSCC hyper-progression and cholestasis.<sup>80</sup> Two treatment-related deaths were reported.<sup>80</sup> Other common AEs that may limit the use of pembrolizumab include gastrointestinal symptoms, rash, fatigue, musculoskeletal pain, diminished appetite, pyrexia, and immune-mediated AEs including colitis, hepatitis, nephritis, pneumonitis, and endocrinopathies.<sup>83</sup>

Notably, in April 2022 the FDA approved a new immunotherapy for the treatment of patients with previously untreated metastatic or unresectable melanoma. The drug, relatlimab, blocks lymphocyte-activation gene 3, an inhibitory immune checkpoint. The drug has shown promise in the treatment of advanced melanoma when combined with

nivolumab, a PD-1 inhibitor. It is worthy to note that many immune checkpoint inhibitors have been first approved for melanoma, preceding studies looking into their efficacy for NMSC, and thus future studies are likely to investigate their role in the treatment of these malignancies.<sup>84,85</sup>

The current 2.2022 NCCN guidelines recommend cemiplimab or pembrolizumab as first-line therapy for the treatment of locally advanced, recurrent, or metastatic cSCC if curative RT or surgery is not feasible.<sup>1</sup> (Table 1) Other treatments such as carboplatin, paclitaxel, epidermal growth factor receptor inhibitors, capecitabine, cisplatin, and 5-FU are now recommended for cSCC only if patients progress or do not respond to checkpoint inhibitors. These treatments were historically the only available options for patients with unresectable disease and are generally associated with significant toxicity and low overall survival rates.<sup>86,87</sup> The guidelines also recommend cemiplimab for patients with BCC previously treated with an HHI or in which an HHI is not appropriate.<sup>75,76</sup> Further studies are currently underway examining the use of immune checkpoint inhibitors for other NMSC indications as well as in the neoadjuvant setting.<sup>88,89</sup> Although there are some reports of efficacy in SOTRs, the safety of PD-1 inhibitors in this population is largely unknown, and the risk for organ rejection with immune activation may be high given the mechanism of action.<sup>90</sup> Nevertheless, patients who may qualify for treatment with immunotherapy benefit from a multidisciplinary approach to care, with input from dermatology, medical oncology, surgical oncology, and radiation oncology.

## Topical Immunomodulators

### Topical Retinoids

Topical retinoids, like their systemic counterparts, also bind to nuclear retinoic acid receptors, affecting the transcription of genes that control cell growth and differentiation.<sup>91</sup> This mechanism of action renders them useful in the treatment of acne, psoriasis, photoaging, and other dermatologic conditions. Topical retinoids have been thought to have immunomodulatory action by normalizing hyperkeratinization and therefore altering the microenvironment of the skin by regulating inflammatory mediators and toll-like receptors, and by inhibiting chemotaxis of polymorphonuclear cells.<sup>92</sup>

Topical retinoids are currently not approved by the FDA for the treatment of NMSC or precursor lesions, however studies have demonstrated efficacy in the treatment of facial AKs. A double-blind, controlled, multicenter study from 1991 involving 1265 patients demonstrated that 0.1% tretinoin cream applied twice daily for 15 months reduced the total number of AKs by 73%.<sup>93</sup>

A more recent RCT from 2003 demonstrated that adapalene gel, a synthetic retinoid, improves AKs, solar lentigines, and other features of photodamaged skin.<sup>94</sup> Ninety patients with AKs and solar lentigines were treated daily with adapalene gel 0.1%, 0.3% or a vehicle gel for 4 weeks, followed by twice daily application if tolerated for up to 9 months. At the end of study period, the mean number of AKs reduced by  $0.5 \pm 0.9$  with 0.1% gel and  $2.5 \pm 0.9$  with 0.3% gel.<sup>94</sup> A significant increase in the number of AKs was observed in the control group ( $1.5 \pm 1.3$ ,  $P < 0.5$ ). Histologic evaluation demonstrated improved cellular atypia in the treatment group, although differences were not statistically significant.

The role of topical retinoids as an adjunct to other topicals has also been explored. A RCT evaluated the efficacy of daily 0.05% topical tretinoin application to AKs following 5-FU cream application.<sup>95</sup> After 3 months, adjunct tretinoin application to the upper extremities showed improved reduction of AKs compared to the control group, suggesting topical retinoids may enhance the efficacy of topical 5-FU in AK reduction.<sup>95</sup> Tretinoin and adapalene have also been used to treat AKs or NMSC in conjunction with laser ablation therapy and PDT.<sup>96</sup>

The efficacy of high dose topical retinoids in preventing NMSC has been investigated, but results supporting chemoprevention are mixed.<sup>97</sup> In one randomized, double-blind, vehicle-controlled study, only 6% of patients had a chemopreventive response when tazarotene was used in patients with basal cell nevus syndrome, suggesting against a clinically significant chemopreventive or chemotherapeutic effect.<sup>98</sup>

Overall, evidence for the use of topical retinoids for the treatment or prevention of NMSC is limited, and other topicals have demonstrated more consistent efficacy for this indication.<sup>99–101</sup> The current 2.2022 NCCN guidelines for the management of cSCC recommends against the use of topical retinoids as prophylactic treatment for patients at high risk of NMSC or AKs.<sup>1,97</sup> The guidelines for BCC note that tazarotene may be considered for treatment,<sup>21</sup> however there is little data to support a significant chemopreventive or curative response<sup>98</sup> (Table 1).

## 5-Fluorouracil

Topical fluorouracil is the most extensively studied topical chemotherapeutic agent and is FDA approved for the treatment of AKs and superficial BCCs.<sup>99–101</sup> 5-FU is an antimetabolite drug that interferes with DNA synthesis by inhibiting thymidylate synthetase activity. Cancerous cells incorporate pyrimidine uracil into RNA more rapidly than normal cells, and 5-FU is misincorporated into nucleic acid, resulting in cell death.<sup>99,102</sup> When combined with calcipotriol, a vitamin D analog, a significant increase in immunity against AKs has been demonstrated among CD4+ T cells.<sup>103</sup> It has been suggested that this robust response in addition to lasting T cell immunity may confer a more durable response when the two medications are used synergistically.<sup>103</sup>

Topical 5-FU has consistently been shown to reduce AKs when applied topically to lesions for 2 to 4 weeks.<sup>104</sup> Two RCTs demonstrated that 5-FU application to the dorsum of the hands<sup>105</sup> and face<sup>106</sup> resulted in a mean reduction of AKs of 70% and 78%, respectively. A recent randomized, double-blinded, placebo-controlled trial published in 2015 compared the application of topical 5-FU cream to a vehicle control twice daily to the face and ears in 932 study subjects who had  $\geq 2$  NMSC in the 5 years prior to enrollment. The treatment group had higher complete AK clearance rates (38% vs 17% at 6 months) and needed fewer spot treatments at 6-month intervals and other follow-ups during the study interval.<sup>107</sup> A systematic review of 4 RCTs assessing 5-FU therapy for AKs published in 2012 showed a total clearance and mean lesion count reduction of 52.6% and 90.2% in the treatment groups, and 0.85% and 28.3% in the vehicle groups, respectively.<sup>108</sup>

Calcipotriol is an inducer of thymic stromal lymphopoietin, a cytokine that produces antitumor immunity in the skin.<sup>109</sup> As discussed previously, when used in combination with 5-FU for the treatment of AKs, a robust T-cell mediated immune response has been shown. An investigator-initiated, randomized, double-blind clinical trial comparing the safety and efficacy of 0.005% calcipotriol ointment + 5-FU cream compared with petroleum jelly + 5-FU cream for a 4 day treatment of AKs on the scalp, face and upper extremities showed a statistically significant 87.8% vs 26.3% mean reduction in the number of AKs in study subjects.<sup>103,109</sup> Data from a systematic review published in 2022 reviewing studies investigating calcipotriol plus 5-FU in the treatment of AKs showed a greater reduction in AKs compared to treatment with 5-FU alone, as well as a lowered risk of cSCC on the face and scalp over a 3-year period.<sup>103,109–112</sup> The lasting effects may be due in part to resident memory T cells conferring long-term protection against AKs and cSCC following T cell activation during treatment.

A recent systematic literature review from 2009 reviewed results from studies investigating the treatment of NMSC with topical imiquimod and 5-FU.<sup>113</sup> Six different studies investigating the use of 5-FU in superficial BCC and cSCC were reviewed. Ninety percent of superficial BCCs were cleared in 31 patients treated for an average of 10.5 weeks with twice daily 5-FU, confirmed 3 weeks after treatment cessation by histologic evaluation.<sup>114</sup> Studies with various regimens of 5-FU application (twice daily, once daily under occlusion, once daily for 1 week then twice daily for 3 weeks, etc.) for various durations (4 weeks – 4 months) showed clearance rates ranging from 26% to 85% of cSCC in situ (SCCIS). The study showing the highest clearance rate of 85% was published in 2003 and data was drawn from 26 lesions that were treated for an average of 7.7 weeks with twice daily 5-FU. In this study, 17 of 26 lesions had histopathologic resolution, 6 were clinically clear and 2 lacked sufficient follow-up.<sup>115</sup> This is one of the highest clearance rates published, and most other studies cite variable clearance rates in the range of approximately 30–60% of SCCIS. Despite promising results, the use of 5-FU in SCCIS is currently not approved by the FDA.

The NCCN guidelines currently recommend topical 5-FU with or without calcipotriol as an accepted treatment modality for the treatment of diffuse AKs, field cancerization and cSCC prophylaxis (Table 1). The NCCN panel currently prefers 5-FU for treatment of AKs over IMI, methyl aminolevulinate (MAL) PDT or IMB given a higher cumulative probability of remaining free from treatment failure.<sup>104</sup> These treatments will be discussed in detail later in this review article. As per the guidelines, topical 5-FU may also be considered for patients with SCCIS, though the cure rate may be lower than that of surgical treatments. Consideration for treatment must also consider the common AEs of treatment which include skin irritation, erythema, dryness, erosions, pain and burning sensations, pruritus, vesicle formation, and ulcerations. Reactions caused by 5-FU monotherapy correlate with the degree of actinic damage present on the treated skin, and therefore patients should be appropriately counseled prior to treatment initiation.<sup>104</sup> Improved

tolerability and milder AEs have been reported when topical 5-FU is used in conjunction with topical calcipotriol to treat precancerous lesions, without reduction in efficacy.<sup>103</sup> The NCCN guidelines for the treatment of BCC recommend consideration of topical 5-FU for patients with superficial BCC with adequate understanding that cure rates may be at least 10% lower than with surgical modalities<sup>21,113,116</sup> (Table 1).

## Imiquimod

IMI is an immunomodulatory drug that activates toll-like receptors, ultimately regulating mRNA expression of genes responsible for the production of cytokines by monocytes, macrophages, and epidermal keratinocytes.<sup>117</sup> The result is an enhanced innate and cell-mediated immune response protective against tumor activity, and induction of pro-apoptotic pathways.<sup>117</sup> IMI is currently FDA approved for the use of superficial BCC (5% IMI) and AKs (all concentrations).<sup>118</sup>

IMI was approved in 2004 for the treatment of superficial BCC after a RCT reported a histologic clearance of 82% for superficial BCC treated topically 5 times per week for 6 weeks. Tumors included in these data were smaller than 2 cm and in low-risk locations.<sup>113,119–121</sup> A more recent meta-analysis from 2012 examining both randomized and nonrandomized studies reported a pooled estimate of 86.2% CR of superficial BCC at 12 weeks post treatment with topical IMI, and a tumor-free survival of 87.3% at 1 year.<sup>122</sup> Studies examining the efficacy of IMI in nodular BCC, including a phase 2 clinical trial, have reported a response rate of 76% after treatment with 5% IMI cream twice daily for 12 weeks.<sup>123</sup> Although surgical approaches remain the standard of care for the treatment of nodular BCCs, IMI may represent an acceptable option for patients who cannot undergo surgery.

Many studies have shown the efficacy of IMI in the treatment of SCCIS, with clearance rates ranging from 70 to 100%.<sup>113,124–127</sup> A double-blind, placebo-controlled RCT reported a 75% clinical and histologic clearance rate at 28 weeks following treatment with 5% IMI daily for 16 weeks.<sup>128</sup> Patients randomized to receive IMI had various local AEs including pruritus, edema, erosions, and drainage. Other studies investigating the efficacy of IMI in SCCIS report high clearance rates, even in SOTRs and patients with CLL treated in combination with 5-FU and sulindac, respectively.<sup>129,130</sup> Generally, studies investigating the efficacy of IMI for SCCIS tumors located on the extremities and the trunk reported improved clearance rates in lower risk anatomic locations.<sup>128</sup> In a study examining 829 patients with a total of 7427 AKs treated with IMI 5% cream three times weekly for 4 weeks, followed by repeat treatment if resolution had not occurred, IMI achieved an 85% reduction in the total number of lesions.<sup>131</sup> Many other double-blind RCTs have reproduced similar results. Further, improved response rates were noted with application three times weekly when compared to twice weekly application.<sup>132–134</sup>

The NCCN guidelines recommend the use of topical IMI for SCCIS in anatomically challenging locations for which recurrences would be small and manageable, with the understanding that cure rates may be lower than with surgical treatment modalities. (Table 1) IMI is also recommended for the treatment of superficial BCC in the NCCN guidelines, citing studies that suggest that IMI use is associated with superior results when compared to 5-FU cream, especially when used on large or truncal tumors.<sup>21,120,122,135,136</sup>

## Ingenol Mebutate

IMB is an extract from the plant *Euphorbia peplus* that induces cell death in dysplastic keratinocytes via necrosis and immune stimulation leading to cytotoxicity.<sup>137,138</sup> Through chemoablation, IMB disrupts the plasma membrane of keratinocytes and leads to mitochondrial swelling. Its additional mechanism of action involves induction of neutrophil infiltration and production of tumor-specific antibodies and pro-inflammatory cytokines, leading to an antibody-dependent cellular cytotoxicity that eliminates residual cells.<sup>117,139</sup>

IMB was first approved by the FDA in 2012 for treatment of AKs of the face and scalp, based on two double-blind RCTs, and later approved for use on the trunk and extremities after data from two further RCTs were published.<sup>140–143</sup> However in 2020, drug production was discontinued in the US and other areas of the world after a study comparing the use of IMB to IMI showed increased rates of cSCC in areas treated with IMB.<sup>144,145</sup>

## NSAIDs

As previously discussed, tumorigenesis in NMSC may be linked to expression of COX-2, thus

supporting the theory that inhibitors of this enzyme may be useful in treatment. Further, as noted previously, NSAIDs may enhance anti-tumor immunity, augment T cell cytotoxicity and improve cancer immunosurveillance.<sup>42</sup>

A RCT of 130 patients published in 1997 studied the tolerability and efficacy of topical 3% diclofenac in hyaluronic acid (HA) gel vs HA gel alone applied twice per day for 24 weeks, and failed to show a statistically significant difference in the reduction of AKs, despite a high rate of PR.<sup>146</sup> In contrast, a more recent multicenter, double-blind, placebo-controlled study showed a statistically significant reduction in AKs in patients treated with 3.0% diclofenac in 2.5% HA gel when used twice daily for 60 days.<sup>147</sup> A second randomized, double-blind, placebo-controlled study produced similar results at 16 weeks after 12 weeks of treatment with twice daily 3% diclofenac in 2.5% HA gel. In this study, there was a 56.1% reduction of AK lesions in the active treatment group, compared to 23.6% in the placebo group.<sup>148</sup>

Given the conflicting results of RCTs, the NCCN guidelines for the management of SCCIS accepts topical diclofenac as appropriate, based only upon lower-level evidence and notes it is inferior to other topical treatments as well for the treatment of AKs. (Table 1) There is no current recommendation for its use in the treatment of BCC.<sup>21</sup>

## Photodynamic Therapy

PDT is efficacious in the treatment of NMSC and AKs by way of the production of reactive oxygen species which cause cellular apoptosis.<sup>149</sup> Application of a photosensitizing agent followed by exposure to light creates the reactive oxygen species and free radicals which contribute to the mechanism of action. There are several different photosensitizers available on the market. The most common are 5-aminolevulinic acid (ALA), and methyl-5-aminolevulinate (MAL). In addition to local effects, PDT has been shown to augment host immune response by way of recruitment of various immune cells to the treated area.<sup>150</sup>

ALA-PDT and MAL-PDT are currently FDA approved for the treatment of AKs. A multicenter, investigator-blinded, randomized, vehicle-controlled study published in 2001 showed 88% clearance of AKs 8 weeks after a single PDT treatment, compared to 6% with vehicle only.<sup>151</sup> A more recent RCT from 2004 showed 89% of patients had a 75% or more clearance rate of AKs at 12 weeks after treatment. Most of the patients enrolled in this trial experienced either a burning or stinging sensation during treatments, and delayed effects such as edema and erythema of the treated sites.<sup>152</sup> Some studies suggest that MAL-PDT may be associated with a shorter duration of pain and discomfort when compared to ALA-PDT.<sup>153,154</sup> An RCT from 2009 evaluating the efficacy of PDT using MAL and light-emitting diodes for the treatment of AKs showed a CR rate of 83.3%.<sup>155</sup> PDT has shown to be effective in delaying the onset of AKs in renal transplant patients when administered at 6-month intervals for 5 years.<sup>156</sup> This may represent an alternative method to reducing the overall actinic burden in SOTRs, however studies looking at the development of cSCC over time in this population treated with PDT are conflicting.<sup>157</sup>

Studies evaluating the efficacy of PDT in the treatment of BCC have shown CR rates ranging from 73 to 99% for superficial BCCs.<sup>153</sup> One study comparing ALA and MAL-PDT for the treatment of nodular BCCs showed similar effectiveness of each,<sup>158</sup> however, others report improved outcomes with MAL-PDT.<sup>159</sup> The results from 2 RCTs showed a CR rate of 73% for the treatment of nodular BCC with MAL-PDT, with the highest effectiveness for lesions of the face (89% CR). Despite variable published efficacy rates, PDT may represent an acceptable non-surgical option for BCCs in patients who cannot undergo surgery. The NCCN guidelines for the treatment of BCC note PDT may have similar effectiveness as cryotherapy but with superior cosmetic outcomes in the treatment of superficial BCC; however, treatment success is inferior to that of IMI.<sup>21</sup>

Data from studies investigating the efficacy of PDT in the treatment of SCCIS have shown response rates of 90–100%, with an average rate of recurrence of 12% following 1 to 3 PDT treatments.<sup>160</sup> A randomized comparison of ALA-PDT to 5-FU in the treatment of SCCIS showed a higher CR in the ALA-PDT group (88%) compared to the 5-FU group (67%).<sup>161</sup> One study evaluated cyclical ALA-PDT treatments for SOTRs at 4 to 8-week intervals for a duration of 2 years and showed a 79 and 95% reduction in cSCCs at 12 and 24 months, respectively, when compared to pre-treatment counts.<sup>162</sup> The current NCCN guidelines for the treatment of cSCC note that PDT treatment may lead to higher rates of initial clearance and durability of response than 5-FU in the treatment of cSCC, however there is significant variability in effectiveness owing to differences in application and protocols. Therefore, 5-FU is still preferred in the treatment of cSCC.<sup>1</sup>

## Discussion

The carcinogenesis of NMSC relies mainly on UV-induced DNA and oxidative damage, which ultimately leads to various mutations in genes regulating cellular growth and proliferation. Among other risk factors for the development of NMSC, immunosuppression has been shown to confer a substantially higher risk, proving the importance of the immune system in the surveillance of these malignancies. It has been suggested that the high mutational burden in NMSC likely leads to the development of UV-induced neoantigens, which in an immunocompetent host, should trigger an active immune response. In those with suppressed immunity, host surveillance mechanisms are impaired, leading to an increased rate of cancer development.<sup>163</sup> It is therefore in accordance that immunomodulatory treatments are often useful in the treatment of NMSC, by way of regulation and activation of the anti-cancer immune response.

At present, there are many immunomodulatory options with various mechanisms of action for the treatment of both AKs and NMSC. The data supports the use of acitretin in the chemoprevention of NMSC in the SOTR population, as well as other individuals with diffuse actinic damage who have been diagnosed with multiple NMSCs.<sup>22</sup> The risk of side effects must be weighed against the potential benefit of preventing the formation of new NMSCs. Other retinoids have less consistent data, or the risk of side effects outweighs the potential benefits.<sup>19,20</sup> Nicotinamide shows promising data as an alternative option for chemoprevention, although long-term studies are needed to investigate the durability of response.<sup>22,24,30</sup> The current data for nicotinamide in immunocompromised populations is generally lacking, making it difficult to generalize the efficacy to these high-risk groups. Given the low rate of side effects and drug–drug interactions, this supplement is generally well tolerated and may be administered to high-risk patients with increased rate of NMSC development. Capecitabine has shown excellent efficacy in the reduction of AKs and cSCC burden, however side effects are common and may be serious. The use of this drug is therefore limited for chemoprevention, but may be an acceptable salvage option in patients with a heavy burden of disease who are not responding optimally to alternative regimens.<sup>38,39</sup> If considered, initiation should occur in a multidisciplinary setting as intensive monitoring is necessary. The use of systemic NSAIDs is generally limited by side effects and risks, as well as the presence of alternatives with superior data to support their use.<sup>54</sup> For SOTRs, revision of immunosuppression from calcineurin inhibitors to mTOR inhibitors should be considered in patients with significant disease burden from NMSC or with aggressive, high-risk, or locally advanced/metastatic tumors.<sup>68</sup> Although surgical approaches remain the standard of care for the treatment of many cSCCs, checkpoint inhibitors (cemiplimab, pembrolizumab) have become a mainstay of therapy in patients with locally advanced, recurrent, or metastatic cSCC if unresectable or not amenable to curative RT.<sup>1</sup> Checkpoint inhibitors also play a role in the treatment of advanced BCCs in select situations. Results from studies examining the utility of checkpoint inhibitors as neoadjuvant treatments are promising and may ultimately lead to a dramatic shift in the standard treatment algorithms for locally advanced and metastatic tumors.<sup>72</sup> Significant toxicity and AEs with the use of checkpoint inhibitors may occur, and the risk of organ rejection is still under investigation.<sup>90</sup> Collaboration with medical oncology, transplant surgery, radiation oncology and surgical oncology is critical in the initiation of these drugs in most circumstances.

Topical immunomodulators are widely used in clinical practice for both the prevention and treatment of AKs and NMSCs. Topical 5-FU is currently accepted as the superior topical therapy for the treatment of diffuse AKs, field cancerization and for the chemoprevention of cSCC given a higher cumulative probability of successful treatment when compared to IMI, MAL PDT or IMB.<sup>104</sup> 5-FU is currently not FDA approved for the treatment of SCCIS or superficial BCC; however, off label use may be considered if surgery or other destructive treatment options are contraindicated or not feasible. The addition of calcipotriol has been shown to result in a greater reduction in AKs, improved tolerability, and a lowered risk of future cSCC development on the face and scalp.<sup>103,109,110,112</sup> IMI is currently FDA approved for the treatment of superficial BCCs and AKs, with the highest BCC clearance rates in truncal tumors. IMI has been shown to be a more effective superficial therapy for BCCs as compared to 5-FU cream.<sup>21</sup> PDT is an efficacious treatment for AKs and is an acceptable and efficacious option for the treatment of cSCC and BCC in patients who cannot undergo surgery. Notably, PDT has been reported to be inferior to IMI in the treatment of BCC especially for large or truncal tumors, however PDT may have better outcomes for elderly patients with lower extremity lesions. For the treatment of SCCIS, PDT has been associated with higher rates of initial complete clearance and higher durable complete response rates when compared to 5-FU.<sup>1</sup> Although a reasonable option for the treatment of certain low risk cSCCs and BCCs, PDT is currently only FDA approved for the treatment of AKs. The data to support the use of topical retinoids as well as NSAIDs is limited and conflicting and given superior alternatives for treatment and prevention of NMSC, their use is currently not recommended.<sup>21–99,101</sup> Diclofenac gel is appropriate to use for AKs due to

a favorable safety profile, however the data supporting its efficacy is weak.<sup>21,164</sup> The use of IMB has been largely discontinued after drug production was discontinued out of concern for increased risk of cSCC.<sup>165</sup>

## Conclusion

The immune system plays a critical role in the surveillance of NMSC, and those who have muted immune responses are at much higher risk for the development of these malignancies. Immunomodulatory therapies enhance the immune response to NMSC through various mechanisms and are critical in both the prevention and treatment of these malignancies. The identification of patients at increased risk for field cancerization and NMSC development is crucial to reduce the overall burden of disease. Proactive approaches to reduce the overall disease burden in the immunosuppressed are necessary, especially in the SOTR population. Once identified, a personalized regimen of both systemic and topical immunomodulators may be selected for at-risk individuals, and close ongoing monitoring should be pursued to prevent morbidity and mortality of NMSC. Cyclical multi-modal therapy regimens over extended periods of times may be necessary and key to reverse UV toxicity to the skin and eradicate neoplastic keratinocytes at risk of tumorigenesis and subsequent morbidity and mortality. With ongoing research into the genetics of cutaneous malignancies and various biomarkers signaling susceptibility to disease, stratification of pre-cancerous lesions, and risk for disease progression, it is likely that the future holds revolutionary options for early detection and personalized treatment.<sup>166</sup> In the present and as our understanding evolves into the future, dermatologists continue to play a critical role in the prevention and management of AKs and NMSCs, and have many immunomodulatory drugs to choose from to individualize regimens for at-risk patients.

## Abbreviations

5-FU, 5-fluorouracil; AKs, actinic keratoses; BCC, basal cell carcinoma; BWH, Brigham and Women's Hospital; CLL, chronic lymphocytic leukemia; COX-2, cyclooxygenase-2; CR, complete response; cSCC, cutaneous squamous cell carcinoma; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FDA, Food and Drug Administration; HA, hyaluronic acid; HHI, hedgehog inhibitor; IMB, ingenol mebutate; IMI, imiquimod; MAL, methyl aminolevulinate; mTOR, mammalian target of rapamycin; NCCN, National Comprehensive Cancer Network; NMSC, non-melanoma skin cancer; ORR, objective response rate; PD-1, programmed cell death 1 receptor; PD-L1, programmed cell death receptor 1 ligand; PDT, photodynamic therapy; PR, partial response; RCT, randomized-controlled trial; RT, radiation therapy; SOTR, solid organ transplant recipients; UV, ultraviolet.

## Disclosure

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