Skin cancer is the most common cancer in the USA. Non-melanoma skin cancers, which include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), comprise the majority. BCC and SCC are commonly treated with surgical excision, curettage, cryotherapy and radiation. Actinic keratoses (AK) are considered precursors of SCC and are commonly treated with 5-fluorouracil, imiquimod, diclofenac, liquid nitrogen or photodynamic therapy. On 5 March 2012 we conducted a Medline search for Phase II and III trials of novel medical treatments that have been reported within the last 3 years. We also searched clinicaltrials.gov to find promising treatments in development. Ingenol mebutate has been investigated as a treatment for AK, SCC and BCC. Dobesilate and the combination of 5-fluorouracil and salicylic acid were also studied for AK. Cetuximab, an EGF receptor inhibitor, was studied for SCC; and vismodegib, a Hedgehog inhibitor, was studied for BCC.

Keywords: 5-fluorouracil/salicyclic acid • actinic keratosis • basal cell carcinoma • celecoxib • cetuximab • dobesilate • ingenol mebutate • squamous cell carcinoma • vismodegib

Skin cancer is the most prevalent malignancy in the USA. More than 3.5 million skin cancers in over two million people are diagnosed annually [1]. Non-melanoma skin cancer composes the majority of cutaneous malignancies.

Basal cell carcinoma (BCC) is the most common form of skin cancer; an estimated 2.8 million are diagnosed annually in the USA [1]. Significant risk factors for BCC include exposure to UV radiation and genetic predisposition [2]. BCC tends to occur in areas of chronic sun exposure, and approximately 74% of cases occur on the head and neck [3]. Worldwide incidence ranges from 407 per 100,000 white men and 212 per 100,000 white women in the USA to two per 100 in certain regions of Australia [4].

BCC was previously thought to arise from multipotent stem cells residing in a specialized part of the hair follicle called the bulge. However, recent evidence suggests that BCC actually arises from long-term resident progenitor cells of the interfollicular epidermis and the upper infundibulum [5]. Although BCC rarely metastasizes, significant morbidity in the form of local tissue destruction and disfigurement can occur [6]. The tumor has the capacity to invade and destroy tissue around it, including healthy skin, nerves, lymphatic and blood vessels, cartilage and bone [7]. Disfigurement may occur if the tumor is left untreated or incompletely removed.

Squamous cell carcinoma (SCC) is the second most common form of skin cancer, with an estimated 700,000 cases diagnosed each year in the USA [1]. Risk factors that apply to SCC include fair skin, excessive cumulative exposure to UV radiation, advancing age, outdoor vocation or recreation, and living in ‘sun belt’ latitudes [8]. The highest risk factors for the development of SCC are the
AK is a common precancerous skin lesion that develops as a result of chronic UV irradiation. AK most commonly affects individuals of Fitzpatrick skin type I or II. AK is usually found on sun-exposed areas such as the face, bald scalp, ears and lateral forearms [11]. AK usually presents as scaly lesions, typically in situ [12,13]. AK is a large proportion of Caucasians with Fitzpatrick skin types 1 and 2, and AK and SCC combined have an estimated prevalence of 40 to 50% of the population aged 40 years and older [14]. AK can occur at younger ages in men, likely because of more occupational and recreational exposure. Recent data from the National Ambulatory Medical Care Survey from 1996 to 2005 showed that 58.9% of patients presenting with AK were male, 98.8% were white and approximately 30% were aged 70–79 years [14]. AK are the third most common reason for consulting a dermatologist in the United Kingdom [15]. AK has been described along with 14.9% of the population in Australia, where the incidence is 15 per 100,000 white men per year, and 26–59 per 100,000 white women per year [16]. AK arises from leukoplakia, radiation AK, scars, chronic dermatitis such as the nose, ear or lip [17]. SCC of the lip or ear metastasizes at rates that range from 10 to 25% [18]. SCC that recurs locally metastasizes at a rate of 25%. AK has a lower incidence of distant metastasis when compared to other cutaneous SCC and has an excellent prognosis with a very low risk of metastasis if treated appropriately. Current treatments can eliminate up to 90% of local tumors [19]. AK is a common precancerous skin lesion that develops as a result of chronic UV irradiation. AK most commonly affects individuals of Fitzpatrick skin type I or II. AK is usually found on sun-exposed areas such as the face, bald scalp, ears and lateral forearms [11]. AK usually presents as scaly lesions, typically in situ [12,13]. 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The sap of Euphorbia peplus has a long history of anecdotal use in treating a variety of disorders including warts, corns and skin cancers, as well as neoplasias of liver, stomach and uterus (Table 1) (44). Serial fractionalizations of E. peplus sap have isolated an actively cytotoxic macriderpine, PEP-005, now known as ingenol mebutate (45).

Current treatments for AK act through either cytotoxic or immunomodulating mechanisms. Ingenol mebutate is unique because it likely acts through both mechanisms, which may be the reason why it works after only 2 to 3 days of treatment (46). It has been proposed that it works in two phases—an acute necrotic phase and a delayed inflammatory phase (46,166). In vitro models have demonstrated that rapid necrosis is mediated by the dissolution of mitochondrial cell membrane potentials. The subsequent decrease in adenosine triphosphate production leads to cell death. The exact process by which ingenol mebutate initiates this process is still under debate, but it may dissolve in the plasma membrane and form vesicles from which Ca2+ is released into the intracellular environment. A rise in intracellular Ca2+ undermines the integrity of mitochondrial membranes and causes cell necrosis within 1 h. The second phase is believed to be mediated by B cells and neutrophils. Necrotic cells release proinflammatory cytokines that stimulate B-cell maturation and production of tumor cell-specific antibodies via PKC. In addition, cytokines lead to the upregulation of endothelial adhesion molecules. Neutrophils migrate to the region and react with antigen–antibody complexes on keratinocytes and release reactive oxygen species. This inflammatory response peaks in approximately 24 h and resolves in 5–10 days (46,166). Siller et al. conducted a multicenter, randomized, double-blind, vehicle-controlled, Phase IIa study of the safety and efficacy of ingenol mebutate as a treatment for AK (47). A total of 58 patients who had at least five biopsy-proven AKs (total number of lesions = 285) were treated with ingenol mebutate gel 0.0025, 0.01 or 0.05% twice, either on days 1 and 2 or on days 1 and 8. Both treatment schedules and all concentrations were well tolerated. Only local skin reactions were reported and included dose-related erythema, scaling, dryness, scabbing and pruritus. Local reactions subside within 1 month and there was no reported scarring or abnormal proliferations. Not surprisingly, 0.05% ingenol mebutate was most efficacious and resulted in complete clinical clearance of 71% of lesions, and 67% of patients experienced clearance of at least 80% of lesions. There was a statistically significant difference between ingenol mebutate 0.05% and vehicle gel in partial clinical clearance (p < 0.0001) and in the number of patients who experienced greater than 80% clinical clearance (p = 0.0185). There was no statistical difference between the two treatment schedules as far as safety and efficacy (46,166).

Anderson et al. conducted a multicenter, randomized, double-blind, vehicle-controlled, Phase IIb study of the efficacy and safety of ingenol mebutate 0.025% applied once-daily for 3 consecutive days and ingenol mebutate 0.05% applied once-daily for 2 or 3 consecutive days (48). In order to be included, patients must have four to eight typical, visible, discrete lesions within a contiguous 25-cm2 field. The treatments were applied to an entire field. A total of 222 patients were included in the analyses. All three treatment regimens were significantly more effective than vehicle gel at reducing the number of AKs on day 57. The partial clearance rates of lesions ranged from 56.0 to 75.4% and were dose-related (p ranged from 0.0002 to <0.0001 vs vehicle gel). Similarly, complete clearance ranged from 40.0 to 54.4% (p ranged from 0.0006 to <0.0001 vs vehicle gel). Local skin reactions included erythema, scaling and crusting, which peaked between days 3 and 8. These reactions resolved within 2–4 weeks of treatment (48).

The results of a large multicenter, randomized, double-blind, Phase IIb study were recently reported by Lebwohl et al. (49). In patients treated on the face and scalp, 42.2% of patients who received ingenol mebutate experienced complete clearance whereas 3.7% in the vehicle gel group experienced complete clearance (p < 0.001). Partial clearance was reported in 63.9% of patients treated with ingenol mebutate and 7.4% of patients treated with vehicle gel (p < 0.001). Local skin reactions included erythema, swelling, pruritus and pain. These reactions were graded and added in order to create a composite score that ranged from 0 to 24 (higher numbers indicating more severe reactions). Local reactions peaked on day 4 and decreased by day 8. The mean highest score induced by an individual using ingenol mebutate was 9.1 ± 4.1, as compared with 1.8 ± 1.6 for the vehicle group. In patients treated on the trunk or extremities, 34.1% treated with ingenol mebutate experienced complete clearance, as compared with 4.7% of patients treated with vehicle gel. Partial clearance was reported for 49.1% of patients treated with ingenol mebutate and 6.9% in the vehicle group (p < 0.0001). The mean maximum local response score per patient for ingenol mebutate group was 6.8 ± 3.5, as compared with 1.6 ± 1.5 for the vehicle group. This was the largest clinical study of ingenol mebutate for treatment of AK to date. Ingenol mebutate was approved by the FDA for the treatment of AK in January 2012. Multiple trials were recently completed that studied the safety and efficacy of ingenol mebutate for the treatment of AK. The results of these studies are yet to be released.

A total of 30 patients completed the trial. Patients who were included had at least one AK on the face or scalp. Lesions were compared based on their grades as determined clinically before the start of treatment. Mild, nonhyperkeratotic lesions were deemed grade I (17.4%), moderate lesions were grade II (45.3%) and severe, hyperkeratotic lesions were grade III (39.1%). Potassium dobesilate 5% cream was approved as a treatment for AK in a preliminary open-label study (41). This study was conducted in patients with AK lesions ≥2 mm in diameter. A total of 11 patients were enrolled and completed the study. Lesions were assessed at baseline and after 2, 4, 6 and 8 weeks, and the mean improvement in grading scores was 64.3% for grade III lesions. These findings are difficult to interpret in the absence of a placebo arm because AK can spontaneously regress. Only local side effects were noted, which included redness, pruritus (22%) and mild stinging (17%). One patient reported erythema outside of the treated area at
Review: Clinical Trial Outcomes

**Low-dose 5-Fu in 10% salicylic acid cream**

Cetuximab was administered as an initial dose of 400 mg/m² and continued as long as the tumor demonstrated response (defined as complete clearance of all lesions as determined by the investigator). Disease control rates (defined as complete response [CR], partial response [PR], stable disease [SD], and disease control [DC]) at 16 weeks were 28.2% (95% CI: 18.1–39.4%) in the cetuximab group and 13% (95% CI: 7.9–20.0%) in the placebo group. At 52 weeks, the disease control rate was 40.0% (95% CI: 29.9–49.8%) in the cetuximab group and 28.1% (95% CI: 18.0–38.3%) in the placebo group. The difference in disease control rate between the two groups was statistically significant (p = 0.002).

The most common adverse events were skin reactions and discomfort. Overall, these effects were comparable between groups and generally consistent with those reported for traditional chemotherapy. A total of 25% of patients in the cetuximab group and 20% in the placebo group experienced grade 3 or 4 skin reactions. The most common grade 3 or 4 skin reactions were skin rash, dry skin, pruritus, and nausea.

In 2009, Hauschild et al. reported the findings of two placebo-controlled Phase III studies of 5-ALA patch (product code PD P306A). Current formulations require long incubation times [56]. In applications of 5-ALA, light application and treated regions need to be protected from light after treatment. The self-adhesive patch can overcome these disadvantages because it can be applied directly to the lesions without the need for ablation before application and treated regions need to be protected from light after treatment. The self-adhesive patch can overcome these disadvantages because it can be applied directly to the lesions without the need for ablation before application and treated regions need to be protected from light after treatment. The self-adhesive patch can overcome these disadvantages because it can be applied directly to the lesions without the need for ablation before application and treated regions need to be protected from light after treatment. The self-adhesive patch can overcome these disadvantages because it can be applied directly to the lesions without the need for ablation before application and treated regions need to be protected from light after treatment. The self-adhesive patch can overcome these disadvantages because it can be applied directly to the lesions without the need for ablation before application and treated regions need to be protected from light after treatment. The self-adhesive patch can overcome these disadvantages because it can be applied directly to the lesions without the need for ablation before application and treated regions need to be protected from light after treatment.
and cryotherapy. Non-surgical approaches include radiotherapy (RT), imiquimod 5% cream, topical 5-Fu and PDT.

Surgical excision is a common method for treating BCC. Primary lesions of any size on the neck, trunk, arms or legs have a 5-year cure rate of more than 99% with surgical excision when completely excised [6]. However, recurrence of the tumor occurs in 21–41% of patients with incompletely excised lesions [65,66]. Mohs surgery is commonly used for patients who present with large (>2cm) tumors, high-risk morphotype BCC, recurrent tumors, or tumors located in cosmetically sensitive locations such as the face [6]. The lowest recurrence rates are obtained with Mohs surgery, with a 5-year recurrence rate of 1.0% for primary tumors and 5.6% for recurrent tumors [6].

Electrodesiccation and current (ED&C) is the most common method used by dermatologists to treat primary nodular and superficial BCC less than 1.5 cm in diameter [6]. Recurrence rates rise dramatically with increasing tumor size [44]. One study showed significantly higher recurrence rates for tumors in the mask area of the face and for tumors greater than or equal to 6 mm in diameter located on the cheek, forehead, scalp or neck [6]. Another disadvantage with ED&C is the potential risk of developing a scar. Alternatively, if selected appropriately, ED&C is an efficacious and cost-effective treatment modality [6].

Cryosurgery is commonly used to treat BCC, but is best reserved for tumors with well-defined borders. The 5-year recurrence rate is 4–17% [44]. Cryosurgery is also associated with adverse outcomes such as pain, tenderness, bulla formation, erythema, sloughing of necrotic tissue and localized edema [6].

RT is a nonsurgical option for patients with primary tumors and superficial BCC less than 1.5 cm in diameter [6]. RT has a cure rate of over 90% for most skin tumors [65]. RT is not recommended for treating early-stage skin cancers in locations where resection would result in a significant cosmetic and/or functional defect [6]. RT has a cure rate of over 90% for most skin tumors [65]. The 5-year recurrence rates are 7.4% for primary BCC and 9.5% for recurrent BCC [6]. RT is not recommended in younger patients because new skin cancers may arise from RT field scars and long-term cosmetic results are poor [71]. Side effects include radionecrosis, atrophy and formation of telangiectasias [71].

Imiquimod 5% is used for AK as described previously and is also FDA approved to treat biopsy-proven, small (<2 cm in diameter), primary, superficial BCC on the trunk, neck, arms or legs of adults with normal immune systems [6]. Imiquimod, applied once-daily five-times per week, has an 82% histologic clearance rate when used to treat BCC [72]. Since long-term clearance rates are not as high as other treatments, it is more commonly used as an adjunctive therapy or an alternative for patients who are not surgical candidates.

Topical 5-FU has been approved by the FDA to be applied twice-daily for at least 6 weeks in the treatment of BCC when traditional methods are not feasible. 5-FU is sometimes used to treat small, superficial BCCs and should only be used on low-risk sites [6]. It generally has low clearance rates compared with other treatment modalities. One study demonstrated that 5-year recurrence rate of 21% when treated with a high concentration, 25% fluorouracil paste [72]. As when used to treat AK, 5-FU is associated with severe local side-effects including pain, burning, pruritus, irritation, inflammation, swelling, tenderness, hyperpigmentation and scarring [72]. PDT is used in the treatment of BCC, typically in cosmetically sensitive areas such as the face. One study of superficial and nodular BCC treated with PDT showed that 89% of lesions cleared with an overall cure rate of 79% after a mean follow-up of 35 months [73]. Side effects associated with PDT include localised effects such as stinging, burning, erythema and edema. Despite relatively good efficacy with PDT, it is a fairly inconvenient treatment option due to the necessity for multiple office visits and the adverse side effects.

Emerging treatments for BCC

**Ingenol mebutate**

Ramsey et al. conducted a Phase I/II clinical trial to examine the efficacy of *E. peplus* sap in treating non-melanoma skin cancer. A total of 36 patients with BCC, SCC and intra-epidermal carcinoma (IEC) were topically treated with 100–300 µl of sap, containing approximately 200 μg ml⁻¹ of ingenol mebutate (Table 2) [144]. They were deemed to be nonsurgical candidates based on the nature or site of the tumor, age, use of anticoagulant drugs or because they had failed previous surgical or topical treatments. A total of 48 lesions were treated with daily treatments for 3 days. Complete clinical response (the absence of tumor on clinical exam) rates at 1 month post-treatment were 82% for BCC, 94% for IEC and 75% or SCC. Partial response was demonstrated in 18% of lesions and these lesions underwent another course of treatment 1 month later. Lesions were re-evaluated between 2 and 31 months later (mean = 15 months) and complete clinical response was seen in 57% of BCC, 75% of IEC and 50% for SCC [144].

**LDE225**

LDE225 – 0.75% cream twice daily over 4 weeks vs vehicle cream

Table 2. Clinical trials of treatments for basal cell carcinoma completed between 2009 and 2012.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients</th>
<th>Results</th>
<th>Most common adverse effects</th>
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<td>Three complete response, nine partial response, one no response</td>
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**Vismodegib (GDC-0449)**

As research continues to implement the aberrant Hedgehog (Hh)-signaling pathway in the carcinogenesis of BCC as well as other neoplasias, new treatments are being developed to target this pathway. Vismodegib is small molecule that has been shown to inhibit the Hh-pathway and is being investigated as a treatment for various cancers [74]. In 2011, the findings of a Phase II trial of vismodegib as treatment for BCC were presented at the European Multidisciplinary Cancer Conference in Sweden [27]. During this trial, 150 mg daily oral dose was administered to 104 patients with advanced disease progressing or intolerable toxicity developed. The trial showed an overall response rate of 43% in locally advanced BCC and 30% in metastatic BCC. In diseases that progressed, an average of 9.5 months without progression was recorded. In 75% of patients taking vismodegib, tumors either regressed or were stabilized. Adverse effects included muscle spasms, hair loss, altered taste, weight loss, fatigue, nausea, decreased appetite and diarrhea. During the study, seven patients died; however, the investigators do not relate their fatalities to vismodegib treatment but rather to their pre-existing disease process [27]. It was approved in January 2012 by the FDA for locally advanced BCC as well as metastatic BCC that are not candidates for surgery or radiation.

**LDE225**

In recent double-blind, randomized,

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**Emerging medical treatments for AK, SCC & BCC**
LDE225 is a topical cream that selectively inhibits smoothened gene expression. It was recently studied in treating nevoid basal cell carcinoma. Ingenol mebutate has been investigated as a treatment for BCC. Two such studies have been published since 2009 and they demonstrated response rates of 65 and 82%.

Emerging treatments for BCC

Surgical approaches include surgical excision (including Mohs surgery) and cryotherapy.

Emerging treatments for actinic keratoses & squamous cell carcinoma

Field-directed treatments include photodynamic therapy, imiquimod 5% cream, diclofenac 3% in hyaluronic acid (HA) gel, and topical 5-fluorouracil (5-Fu) in varying strengths.

Lesion-directed treatments include surgical excision, curettage, cryotherapy and lasers.

In the USA, the prevalence of non-melanoma skin cancer is of considerable interest. A recent study conducted by Skvarla et al. demonstrated that non-melanoma skin cancer is the most common cancer in the United States, with an incidence of 176 per 100,000 people.

Current treatments for BCC & SCC are paramount for patients with disease that are refractory to current treatment, or unable or unwilling to undergo surgery. One of the most promising avenues of research targets various aspects of the Hh-signaling pathway. Recent FDA approval of the Hh-pathway inhibitor vismodegib for the treatment of BCC opens a new and exciting avenue for establishing pharmacological therapies. Over the next few years, it is anticipated that this drug from current studies will be published and further potential therapeutic options can be reassessed.

Dobesha, F-S/UA and cetuximab hold promise, but the number of studies is limited. More studies and trials with larger samples will further elucidate if these drugs will be good alternatives in the future.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony; grants or patents received or pending, or royalties.

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References

Full list of references available in the manuscript.

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Emerging treatments for AK, SCC & BCC


Excellent analysis of the literature regarding 5-fluorouracil in the treatment of actinic keratoses.


