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Cutting Edge in Medical Management of Cutaneous Oncology

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Abstract

Traditional chemotherapy has resulted in only a modest response if any for the three most common cutaneous malignancies of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. Recent advances in understanding of the defects in the pathways driving tumorigenesis have changed the way that we think of these cancers and paved the way to targeted therapy for specific tumors. In this review, we will introduce the novel systemic treatments currently available for these cancers in the context of what is understood about the tumor pathogenesis. We will also introduce ongoing studies that will hopefully broaden our options for highly effective and tolerable treatment.

Keywords

Melanoma; basal cell carcinoma; squamous cell carcinoma; chemotherapy; pathway inhibitor; immunotherapy

INTRODUCTION

The objective of this review is to discuss the novel systemic treatments available for the management of metastatic basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. Although surgical excision is the gold standard treatment for all of these cutaneous malignancies, extensive locally destructive or metastatic disease still poses a therapeutic challenge and treatments are rarely curative. Traditional treatment is highly toxic and the non-specificity of the mechanism of action makes it impossible to determine who will respond to treatment. The advent of molecular targeted therapy is changing the

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therapeutic landscape for these diseases with increased therapeutic index and in many cases with a more tolerable toxicity profile.

Basal Cell Carcinoma

BCC is the most common form of skin cancer with an incidence rate that is 4 to 5 times more likely than SCC. It is typically slow-growing, but if left untreated local invasion may occur, leading to destruction, disfigurement, and rarely metastasis. The options available for treatment of local disease include surgery, destruction, radiation, topical immunomodulation, and topical chemotherapy. Locally advanced BCC may invade underlying muscle, bone, or other contiguous structures. Metastatic disease is rare but can be life threatening. In those cases in which local modalities are insufficient, systemic therapy is warranted. There have been variable successes with cisplatinum-based chemotherapy regimens in the past.[1]

Recent advances in the understanding of the pathogenesis of BCC have led to the development of therapeutics targeting the biological mechanism driving this malignancy. The Hedgehog (Hh) pathway has been shown to play a key role in the pathogenesis of BCC with the majority of BCC bearing mutations in genes in this developmental pathway. The majority of mutations implicated in BCC pathogenesis involve mutations in the transmembrane proteins with loss of function of patched homologue 1 (Ptch1) or gain of function of smoothened homolog (Smo).[2] Mutation in the Ptch1 gene was initially implicated as the cause of the rare autosomal dominant heritable basal cell nevus syndrome (Gorlin syndrome), the hallmark of which is a high susceptibility for the development of BCCs.[3-4] It was later found that essentially all BCCs harbored mutation in the Ptch1 gene or other alterations in the Hh signaling pathway.[5]

Ptch1 is a keratinocyte membrane protein that binds Sonic Hedgehog. In the absence of Sonic Hedgehog, the role of normal Ptch1 is to inhibit Smo. Smo enables the activation of a family of transcription factors called Gli which then enter the nucleus to promote expression of more Gli, Ptch1, as well as other apoptotic factors, and suppression of genes associated with keratinocyte differentiation. This sequence of events leads to cell proliferation and increased survival.

Overexpression of Ptch1, Smo, Gli1, and Gli2 are associated with BCC.[6] This makes the Hh pathway both an attractive and logical target for molecular inhibitors for treatment of BCC. A number of hedgehog pathway inhibitors (HPI) are under development in both oral and topical formulations. Currently, all are HPI against Smo.

Vismodegib (Genentech/Roche), previously known as RG3616 or GDC-0449, is the first of the oral small molecule HPI against Smo to be FDA approved for locally advanced or metastatic BCC. In phase I testing, 18/33 patients with locally advanced or metastatic BCC showed a response to the drug and 11 treated patients had stable disease (SD) over a median follow-up of 9.8 months. Measurement of Gli in treated tumors was lower, demonstrating a down-regulation of the Hh pathway thus confirming the molecular mechanism of action.[7] In a phase II trial, looking at locally advanced BCC not amenable for surgery or radiation and metastatic BCC, the overall response rate (ORR) was 43% in the locally advanced group and 30% in the metastatic group. The median duration of progression-free survival (PFS) for both groups was 9.5 months.[8]

LDE225 (Novartis) is another oral HPI targeting Smo. In a phase I dose-escalation study in solid tumors, LDE225 was found to have a dose-dependent inhibition of the Hh pathway, which was measured by downregulation of Gli-1 expression. Although the trial was not designed to test for efficacy, it is notable that only 1 of 7 subjects with BCC progressed

while on treatment.[9] Phase II trials are currently underway. Other systemic HPIs are currently in development. These include IPI-926 (Infinity Pharmaceuticals), TAK-441 (Millennium Pharmaceuticals), PF-04449913 (Pfizer), LEQ506 (Novartis), and BMS-833923 (Bristol-Myers Squibb).

Topical delivery of HPIs is also under investigation and poses an attractive option in terms of side effect profile. CUR61414 (Curis/Genentech/Roche), was shown to be effective in preclinical models but failed to have clinical activity in superficial or nodular BCCs in a phase I clinical study in humans.[10] LDE225 was also formulated as a topical cream. In a randomized, vehicle-controlled, intra-individual trial in subjects with basal cell nevus syndrome, topical LDE225 resulted in clinical responses in 12 of 13 BCCs studied, while tumors treated with vehicle alone showed no efficacy.[11] Although these are promising results, further studies will be needed to test if the findings are generalizable for patients with BCC without the syndrome.

Locally advanced and metastatic BCC portends a grave prognosis. The standard of care remains the cisplatin-based chemotherapy. However the landscape of treatment for BCC is on the cusp of changing with the advent of HPIs and targeted molecular approach to treatment and hopefully the prognosis for advanced disease will improve as well.

Melanoma

Melanoma is a devastating disease once metastatic and is the leading cause of skin cancer death.[12] Systemic treatment for metastatic melanoma includes chemotherapy, immunotherapy, and more recently targeted therapy. Chemotherapy has been the standard of care for stage IV non-resectable melanoma with only a modest response and no improvement in overall survival.[13] With the advent of targeted therapy, we now understand melanoma to be a heterogeneous entity with responses to treatment dependent upon genetic status. Therefore, management of systemic disease now necessitates obtaining genetic analysis prior to a discussion of the options available for an individual patient.

Immunotherapy—Immunotherapy has long been known to play an important role in controlling melanoma and has been used in the adjuvant setting. Interferon alpha 2b and more recently GM-CSF have been shown to improve progression-free and overall survival in high-risk melanoma in the adjuvant setting. For metastatic melanoma, immune therapy options include interleukin-2, ipilimumab, and interleukin-12.

High dose interleukin-2 can be highly efficacious in a very limited subset of patients with an ORR of 16% and 6-8% complete response rate.[14] However, it causes significant toxicities and adverse events requiring intensive monitoring such as hypotension, renal insufficiency, hepatocellular damage, edema, respiratory compromise, myocardial infarction, sepsis, and death. Given the side effect profile, it is often a treatment reserved only for young and fit patients.[15] There are currently no biomarkers to determine who could likely benefit from treatment, however it has been found that patients with disease limited to subcutaneous tissue and those who are able to receive more dosages have been more likely to achieve an objective response.[16]

Ipilimumab (Bristol-Myers Squibb) is a CTLA-4 antibody and has been recently FDA approved for the treatment of metastatic melanoma. CTLA-4 competes for binding of a surface protein B7, thus inhibiting T-cell proliferation and release of immune stimulatory cytokines. Ipilimumab blocks CTLA-4, thus taking the proverbial brakes off the immune system and allowing the immune system to act against melanoma.[17] In a phase 3 study comparing ipilimumab, with or without glycoprotein 100 (gp100) peptide vaccine, to gp100 alone in patients with previously treated melanoma, there was a statistically significant

improved survival associated with treatment with ipilimumab. Median OS in the ipilimumab groups were not different and was about 10 months compared to 6.1 months for the gp100 alone group. A major drawback of this treatment has been the lag in treatment response.[18]

IL-12 is a heterodimeric cytokine that regulates both innate and adaptive immune response.[19-20] It has been shown to enhance the killing of tumor cells by tumor-infiltrating lymphocytes in patients with melanoma.[21-22] Local delivery of IL-12 via direct intratumoral injection of IL-12 plasmid DNA is well-tolerated and has been shown to result in local effects in the treated tumor but no systemic effect.[23] Phase I and II trials of systemic IL-12 have been reported with responses in melanoma but is associated with significant toxicity.[24-26] More recently, a phase I study of intratumoral electroporation of a DNA plasmid expressing IL-12 into melanoma lesions has been shown to result in regression of untreated metastases in 10 of 19 evaluable patients and is not associated with significant side effects.[27] Future studies are proposed.

Although immunotherapy has been shown to make an impact in melanoma beyond just the adjuvant setting, it is still poorly understood why subsets of patients have better response than others. Further investigations will need to be made to determine why responders respond and possibly what can be done to convert a non-responder to a responder. As targeted therapies become the standard of care in melanoma, immunotherapy has become second line treatment reserved for patients who have failed targeted treatment or for those who do not qualify for targeted treatment. Studies are underway combining immunotherapy with targeted therapy such as vemurafenib, a BRAF inhibitor, to potentially boost the efficacy of both.

Therapies targeting molecular signaling—There are 2 main pathways currently recognized to play a role specifically in melanoma pathogenesis. These are the mitogen activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K) pathway. Recognizing these pathways and developing drugs that target specific points that are dysregulated in the pathways have several advantages. The specificity allows for targeted treatment with fewer side effects. And because responders are chosen based on their genetic status, it becomes possible to predict clinical response without subjecting non-responders to treatment that will not be effective for them.

MAPK Signaling Pathway—MAPK signaling is initiated by binding of receptor tyrosine kinases, which then lead to activation of Ras, a small G protein on the inner surface of the cell membrane. Once activated, Ras can form complexes with Raf, which then leads to phosphorylation of ERK via activation of MEK. ERK can directly enter the nucleus and effect translation of genes and control cellular proliferation.[28]

BRAF—Mutation in the BRAF gene occurs in about 66% of melanoma tumors and are commonly found in non-chronically sun-exposed skin.[29] BRAF mutation is uncommon in acral-lentiginous melanoma, but we have observed several cases bearing the BRAF mutation at our institution. The BRAF mutation confers increased kinase activity that can lead to increased tumor proliferation.[30] Inhibition of the mutated BRAF gene has been shown to be the most effective treatment for melanoma at this time and should be considered first-line treatment for melanoma bearing this mutation. In a recently published phase III trial of oral vemurafenib (Genentech/Roche), a new recently FDA approved BRAF selective inhibitor for metastatic patients bearing the BRAF V600E mutation, showed a 48% response rate for vemurafenib compared to a 5% response rate for dacarbazine. A 6-month interim analysis showed a 63% reduction in risk of death and a 74% reduction in risk of death and disease progression in the vemurafenib versus the dacarbazine group (P<.0001 for both comparisons). Another favorable aspect of treatment with vemurafenib is its relatively

benign side effect profile.[31] Common side effects of vemurafenib include rash, fatigue, arthralgia, alopecia, photosensitivity, nausea, diarrhea, keratoacanthoma or SCC and to a lesser extent liver function abnormalities and renal insufficiency.

The recent FDA approval of vemurafenib has changed the landscape for management of metastatic melanoma and has caused significant excitement in the melanoma community. Unfortunately, what is not clearly understood is why there is variable response to the medication despite presence of the BRAF mutation, implying that other important factors play a role in melanoma tumorigenesis. Also, among the initial responders, most patients eventually progress on treatment. Some mechanisms of resistance have been proposed but have thus far not been validated.[32]

MEK—MEK is a downstream target of Raf in the signaling cascade. It has been shown to have mixed results in melanoma. A phase I trial with AZD6244 (AstraZeneca) showed tumor shrinkage in 6 out of 11 patients.[33] However a subsequent phase II trial showed PR in some patients, mainly those with BRAF mutations, but there was no benefit in PFS when compared to temozolomide, which is an oral alkylating chemotherapy commonly used in melanoma.[34] MEK in combination with temozolomide, docetaxel, or temsirolimus has been shown to be associated with tumor regression in only BRAF mutants and delayed progression in BRAF and NRAS mutants.[35] This suggests possibly that MEK plays a bigger role in tumorigenesis in BRAF mutants than NRAS mutants. Studies are currently underway comparing AZD6244 in combination with dacarbazine (in BRAF mutant melanoma only)[36] or docetaxel versus chemotherapy alone.[37] Two other studies hope to compound the MEK inhibiting effects of AZD6244 by targeting parallel growth pathways with an mTOR and VEGF inhibitor temsirolimus (BRAF mutant melanoma only)[38] or a VEGF inhibitor cediranib.[39] A newer MEK inhibitor GSK1120212 is currently under investigation in a phase I trial in combination with a BRAF inhibitor GSK2118436 for metastatic BRAF mutant melanoma.[40] It is showing great promise, indicating possibly that dual targets in the same pathway are more effective than a single one.

PI3K/AKT Pathway—The PI3 kinase (PI3K) pathway is a prosurvival pathway, antagonizing apoptosis. PI3K is activated by growth factor receptors. It has 2 actions: to regulate cell proliferation via control of entry into the cell cycle and to activate AKT via PDK1. AKT then directly activates transcription factors that cause transcription of prosurvival genes. The PI3K/AKT pathway is constitutively activated in melanoma although mutations in AKT are found in only a small proportion of melanomas.[41] Mammalian target of rapamycin (mTOR) is a serine/threonine kinase downstream in this pathway that leads to increased cell growth. Increased activation of mTOR was found in 73% of melanoma cell lines.[42] This pathway can be opposed by PTEN.[43] Mutation in PTEN has been found in 11% of melanoma tumors[44] and 43% of melanoma cell lines.[45] A number of inhibitors of this pathway are in the early stages of development, all targeting this pathway from different angles. Thus far, none of the inhibitors of this pathway have demonstrated an objective response.

Perifosine (Aeterna Zentaris) is an AKT inhibitor, inhibiting AKT phosphorylation and translocation to the cell membrane. Unfortunately, a phase II trial using this drug in metastatic melanoma showed only stabilization of disease in 3 out of 14 patients and was associated with side effects requiring missed, delayed, or reduced dose in all patients.[46]

UCN-01 (Kyowa Hakko Kogyo) is an inhibitor of PDK-1, whose role is activation of AKT thus leading to decreased apoptosis. A phase I trial demonstrated PR in one patient on this medication. A subsequent phase II trial of UCN-01 in metastatic melanoma accrued 16

evaluable patients with 4 patients demonstrating SD and 12 progressive disease. Median PFS was 1.3 months and median OS was 7.3 months. It was relatively well-tolerated.[47]

Various mTOR inhibitors are also being evaluated in patients with melanoma. Temsirolimus, CCL-779, (Wyeth) is an mTOR inhibitor that has been tested in a melanoma phase II clinical trial with disappointing results with only one PR lasting just 2 months.[48] Everolimus (Abbott) is another mTOR inhibitor with dual activity against EGFR. It is currently under investigation in a phase II trial which has thus far demonstrated 7 out of 24 patients with stabilization of disease in an interim analysis.[49]

Dual pathway inhibition—It is believed that both the MAPK and the PI3K/AKT pathways play key roles in melanoma tumorigenesis. Inhibition of the PI3K/AKT pathway alone has been disappointing without objective response. Raf inhibition, on the other hand, is limited to those bearing the BRAF mutation and is not durable in the majority of cases. There is hope that using a combinatorial approach with inhibitors in both pathways will have an additive positive effect. In cell culture, the combination of sorafenib, a non-selective Raf inhibitor, with sirolimus, an mTOR inhibitor, caused a two-fold increase in apoptosis of melanoma cells relative to sorafenib alone. This was attributable to an upregulation in genes associated with endoplasmic reticulum stress-induced apoptosis.[50] BEZ235 (Novartis) is another molecule with dual mTOR and PI3K inhibition that has shown greater activity than temsirolimus in preclinical melanoma models.[51] There is also currently a phase Ib study underway combining BEZ235 with the MEK inhibitor MEK162.[52]

KIT—Kit is a cytokine receptor that belongs to the type III receptor tyrosine kinase family. Kit signaling plays an important role in a number of physiological processes including melanogenesis.[53] Overall, this mutation is rare but is most commonly found in melanoma located on chronically sun-damaged skin, mucosa, and acral skin.[54] The overall incidence rate of Kit mutant melanoma has been reported to be 8%.[55]

Imatinib (Novartis) was the earliest Kit inhibitor tested in clinical trials for melanoma. Two previous trials in which imatinib was tested for efficacy against melanoma demonstrated no treatment response.[56-57] However, it is important to note that the patients were not tested for Kit mutation and it was determined that most selected patients had tumors that demonstrated little to no Kit expression by immunohistochemistry. A recent phase II open-label, single-arm trial using imatinib only in Kit mutant metastatic melanoma recruited a total of 43 patients and resulted in 23 CR, 13 PR, and 10 patients with SD. The median PFS was 3.5 months.[58] Based on this study, it can be concluded that Kit inhibitors can play an important role in the armamentarium against selected melanoma bearing this mutation. Multiple trials are ongoing using newer tyrosine kinase inhibitors such as nilotinib, sunitinib, dasatinib, and masitinib against Kit mutated melanoma.

c-MET—c-Met is a receptor tyrosine kinase that is activated by its ligand hepatocyte growth factor and is essential for normal development, cell migration, growth, survival, differentiation, and angiogenesis.[59] In normal skin, c-Met is expressed on epithelial cells and melanocytes, whereas hepatocyte growth factor is produced mainly by mesenchymal cells and interacts with c-Met in a paracrine manner.[60] c-Met has been found to be expressed in 88% of melanomas[61] with overexpression correlating with the invasive growth of melanoma cells. Many melanomas also secrete hepatocyte growth factor, which can induce sustained activation of c-Met in an autocrine fashion.[62] Cabozantinib, XL184, (Exelixis) is a c-Met and VEGFR2 inhibitor found in a phase II randomized discontinuation trial of patients with advanced solid tumors that demonstrated a 5% objective response rate in melanoma. Patients with bony metastases from pancreatic, breast, or melanoma had an objective response of 87%.[63] Cabozantinib is currently in a phase II trial among patients

with various solid tumors, including melanoma.[64] Foretinib, XL880, (GlaxoSmithKline) is another c-Met/VEGFR2 inhibitor that also has shown some objective response activity in patients with melanoma in a phase I trial.[65]

Epidermal Growth Factor Receptor—The epidermal growth factor receptor (EGFR) is a member of a family of transmembrane protein kinase receptors which consists of the 4 receptors: EGFR (HER1 or ErbB1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4).[66] The EGFR gene resides on chromosome 7. Several different ligands activate these receptors, which then relay signals to the parallel MAPK and PI3K pathways leading to growth effects, angiogenesis, migration, and invasion. EGFR has been shown to play an important role in the growth and survival of many tumors including cutaneous malignancies. Anti-EGFR agents are monoclonal antibodies directed at the extracellular domain of the receptor and low-molecular weight adenosine triphosphate (ATP)-competitive inhibitors of the receptor's intra-cellular tyrosine kinase (TKI).

ErbB1 has been found to be expressed in up to 96% of primary melanomas and in 90% of metastatic tumors.[67] There are gains in chromosome 7, where EGFR resides, in about 50% of melanomas, and increased copy number of chromosome 7 has been associated with poor prognosis in some studies.[68-69] ErbB3 is also frequently expressed in melanoma and has been associated with tumor progression and a worse prognosis.[70-72] Evidence of the importance of EGFR signaling has been seen in melanoma cell lines[70] as well as in animal models.[73] A screen for somatic mutations in ErbB4 revealed that 19% of metastatic tumors harbored this mutation.[74]

The ErbB1 inhibitor erlotinib hydrochloride (Genentech) has been evaluated in a phase II trial of metastatic melanoma and showed no objective responses, but 4 of 14 patients had SD.[75] The ErbB1/B2 inhibitor lapatinib is currently under investigation for melanoma bearing the ErbB4 mutation after preclinical data suggests its effectiveness in ErbB4 mutant melanoma. The ErbB1/B2 inhibitor gefitinib (AstraZeneca) was tested, and only 2 of 50 evaluable patients had PR.[76] A trial of erlotinib hydrochloride in combination with the vascular endothelial growth factor A inhibitor bevacizumab (Genentech/Roche) showed greater efficacy, with 2 of 23 patients having PR lasting less than 6 months and 5 patients having SD lasting greater than 6 months.[77] Toxic effects were greater with this combination, with 1 patient each experiencing myocardial infarction and bowel perforation.

Vascular Endothelial Growth Factor Receptor—Angiogenesis plays a major role in tumor growth. Targeting the vascular endothelial growth factor receptor (VEGF) makes logical sense and has been shown to affect tumor growth by inhibition of angiogenesis. Although this is considered targeted therapy, it does not specifically target melanoma cells. Among the VEGF inhibitors, Bevacizumab is perhaps the most extensively studied anti-VEGF antibody. It is under investigation in combination with immunotherapy, chemotherapy, and other targeted treatments in metastatic melanoma. It appears to have a synergistic effect when used in conjunction with other systemic modalities.

Bevacizumab with immunotherapy—Phase II trial of bevacizumab and high-dose interferon alpha-2b, which has antiangiogenic properties via down-regulation of basic-fibroblast growth factor, in metastatic melanoma resulted in a median PFS of 4.8 months and OS of 17 months as compared to historical control of bevacizumab alone with PFS of 3 months and OS of 8.5 months. Six patients had PR and 5 patients had SD for greater than 24 weeks.[78] In a phase I trial of bevacizumab and ipilimumab for stage III or IV melanoma, of the 21 patients who were evaluable, there were 8 PR, all of whom had durable responses greater than 6 months, and 6 SD. Post-treatment biopsies showed activated vessel endothelium with extensive T-cell trafficking, which were not seen in patients treated with

ipilimumab alone. These results suggest a synergistic effect of VEGF and CTLA4 blockade.[79]

Bevacizumab with chemotherapy—There have been many trials looking at bevacizumab used in conjunction with various chemotherapeutic regimens which include temozolomide, nab-paclitaxel, carboplatin/paclitaxel, and dacarbazine. They have shown a modestly improved PFS and/or OS relative to previously reported survival for bevacizumab alone.[80-84]

Bevacizumab with other targets—It is still too early to say that bevacizumab has a synergistic effect when used in conjunction with other targeted treatment. In a phase II trial of bevacizumab and everolimus, median PFS was 4 months and OS was 8.6 months.[85] A triple combination trial of temozolomide, sorafenib (Raf kinase inhibitor), and bevacizumab of 11 patients with refractory acral advanced melanoma, resulted in 1 CR, 2 PR, and 6 SD.[86] However an interim report of another triple combination regimen of bevacizumab, oxaliplatin, and sorafenib in a phase I/II trial accruing 6 patients showed 1 PR, 3 mixed response, and 3 progression of disease.[87] Additionally, there are trials ongoing combining dasatinib and bevacizumab.

Ranibizumab—Ranibizumab (Genentech) is a monoclonal antibody fragment derived from the same parent mouse antibody as bevacizumab. It is much smaller than the parent molecule and has been affinity matured to provide stronger binding to VEGF-A. There are currently multiple trials using this molecule for choroidal and uveal melanoma as an adjuvant for tumor control or for control of radiation retinopathy or maculopathy.

Squamous Cell Carcinoma

SCC has been shown to have an increased expression of EGFR, with about 92-100% of SCC demonstrating binding to EGFR antibody.[88-89] High EGFR signaling has been associated with aggressive disease, poor response to therapy, increased development of resistance to cytotoxic chemotherapy, poor survival, and poor prognosis.[90] Another study found that primary SCC tumors were immunohistochemically focally weakly positive for EGFR while metastatic SCCs were diffusely strongly positive, suggesting that stronger expression of EGFR had a higher potential for metastasis.[91]

Cetuximab (Merck) is an anti-EGFR monoclonal antibody approved by the FDA for SCC of the head and neck. It binds with higher affinity than natural ligands TGF-α and EGF. Cetuximab inhibits progression in the cell cycle at the G0/G1 phase, increases expression of the cell cycle regulator p27KIP1, and induces apoptosis by increasing expression of pro-apoptotic proteins or by inactivation of anti-apoptotic proteins.[92] It can also inhibit angiogenesis via inhibition of VEGF, interleukin-8, and basic fibroblast growth factor.[93] Cetuximab has been shown to be effective in case reports for recurrent non-resectable squamous cell carcinoma as well as metastatic disease.[94-96] There have been several phase I and II trials using cetuximab in combination with platinum-based chemotherapy documenting safety and efficacy in the combination regimen in metastatic, recurrent, or refractory SCC of the head and neck.[97-99] However, larger studies have not been done documenting effectiveness as a monotherapy. Predictive biomarkers for success with cetuximab include presence of EGFR in the tumor and wild-type for K-Ras[100] and BRAF[101]. The rationale is that these mutations constitutively activate the downstream MAPK pathway that is independent of EGFR activity.

Panitumumab, ABX-EGF, (Amgen) is a human IgG2 monoclonal antibody against EGFR that binds to EGFR like cetuximab. Phase I trials have shown it to be well-tolerated and

efficacious in colorectal carcinoma and non-small cell lung cancer. An open-label phase II trial is currently underway to study the clinical efficacy in SCC. Matuzumab, EMD 72000, (Merck/Takeda) is a humanized IgG1 monoclonal antibody against EGFR. It has been shown to have tumor response against esophageal SCC, cervical carcinoma, ovarian carcinoma, colorectal carcinoma, and head and neck SCC.[102] A phase II trial of matuzumab in patients with platinum-resistant ovarian carcinoma showed that matuzumab was well-tolerated and demonstrated evidence of anti-tumor activity.[103] There are currently no studies at this time using this drug in the treatment of non-melanoma skin cancer.

EGFR TKI and Non-melanoma Skin Cancer

TKIs are synthetic low molecular weight molecules that interact with the intracellular tyrosine kinase domain of several receptors including EGFR. They inhibit ligand-induced receptor phosphorylation by competing for intracellular Mg-ATP-binding sites.[104] Gefitinib has been shown to inhibit EGFR and MAPK activation and Pak 1 activity in exponentially growing cutaneous squamous carcinoma cells. It has been approved for the treatment of non-squamous cell lung cancer after platinum-based or docetaxel based therapy failure and has been shown to have modest activity in advanced skin SCC.[105] Erlotinib is a potent reversible, selective inhibitor of EGFR (ErbB1)[106] which is also approved for non-squamous cell lung cancer but has demonstrated effectiveness in other cancers as well.[107] There are several studies underway to investigate its utility in cutaneous SCC in combination with radiotherapy, as an adjuvant, or as a neoadjuvant therapy.

Conclusion

Management of cutaneous malignancy has entered a new era. Understanding the molecular basis for tumorigenesis has paved the way towards development of new molecules that inhibit at critical sites necessary for neoplastic growth and survival. Some agents have shown startling efficacy and yet others have equally surprised with their lack of efficacy, making the poignant message that although the frontier of our understanding has advanced significantly, the entire story is yet to be told.

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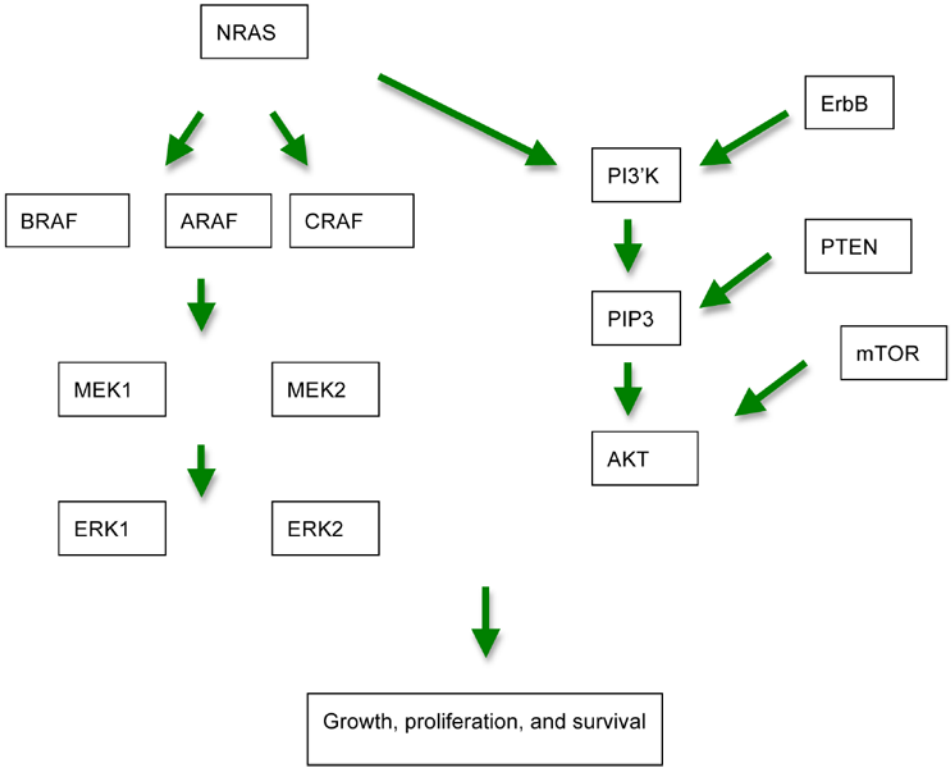

Figure 1.
Simplified schematic for pathways involved in melanoma tumorigenesis.

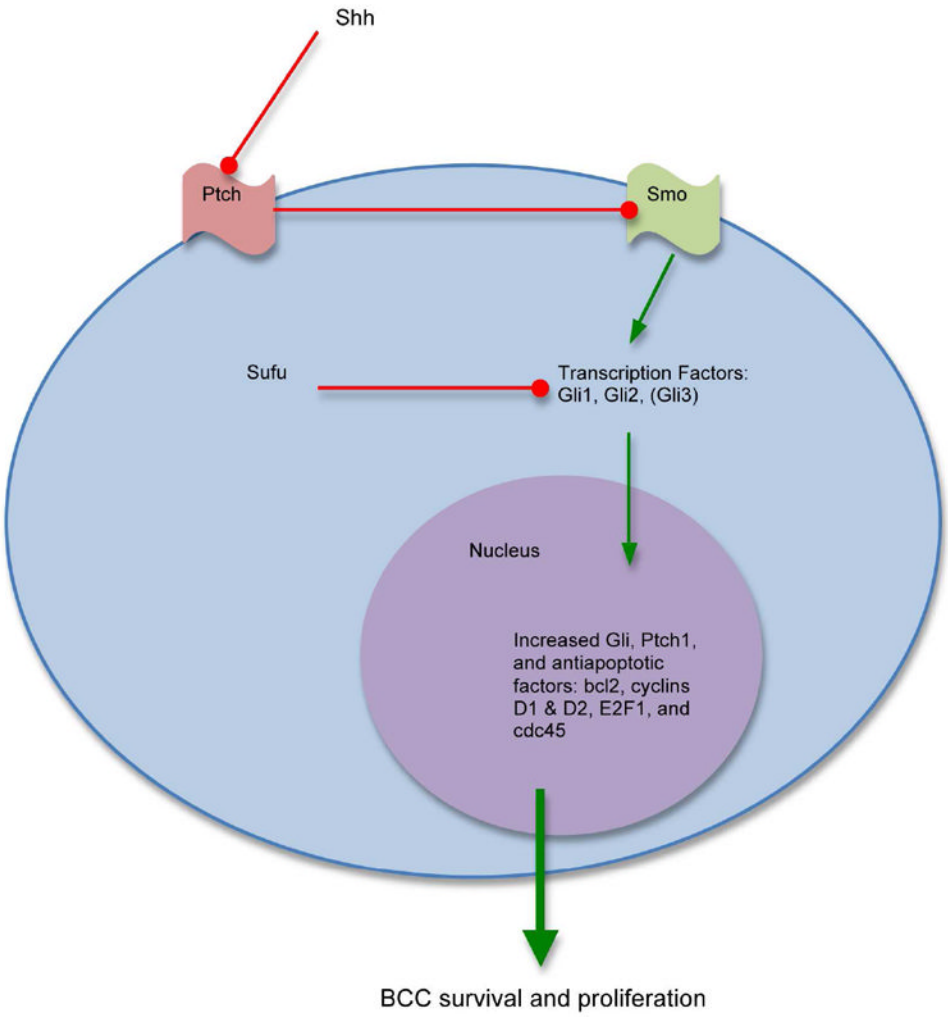

Figure 2.
Hedgehog pathway in the pathogenesis of basal cell carcinoma.

Systemic Therapy for Melanoma

Class	Medication	Mechanism of action
Immunotherapy	High dose IL-2	IL-12 mediated killing of tumor via tumor-infiltrating lymphocytes
	Ipilimumab	CTLA-4 antibody
	Intratumoral electroporation of IL-12	Gene transfer using in vivo DNA electroporation of IL-12 leading to IL-12 mediated killing of tumor
Targeted therapy	Vemurafenib	BRAF inhibitor
	GSK118436	BRAF inhibitor
	Sorafenib	Non-selective RAF inhibitor
	Selumetib (AZD6244)	MEK inhibitor
	GSK1120212	MEK inhibitor
	MEK162	MEK inhibitor
	Sirolimus	mTOR inhibitor
	Temsirolimus (CCL-779)	mTOR and VEGF inhibitor
	Everolimus	mTOR and VEGF inhibitor
	BEZ235	mTOR and PI3K inhibitor
	Cediranib	VEGF inhibitor
	Perfosine	AKT inhibitor
	UCN-01	PDK-1 inhibitor
	Imatinib	KIT inhibitor
	Nilotinib	KIT inhibitor
	Sunitinib	KIT inhibitor
	Dasatinib	KIT inhibitor
	Masitinib	KIT inhibitor
	Cabozantinib (XL184)	c-MET and VEGFR2 inhibitor
	Foretinib (XL880)	c-MET and VEGFR2 inhibitor
	Gefitinib	ErbB1/B2 inhibitor
	Bevacizumab	EGFR inhibitor
	Ranibizumab	Monoclonal antibody fragment VEGF-A inhibitor

Systemic Therapy for Squamous Cell Carcinoma

Medication	**Mechanism of action**
Cetuximab	EGFR monoclonal antibody
Panitumumab	IgG2 monoclonal antibody against EGFR
Matuzumab	Humanized IgG1 monoclonal antibody against EGFR
Gefitinib	EGFR TKI
Erlotinib	ErbB1 inhibitor