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# New Horizons in the Treatment of Basal Cell Carcinoma

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# A Primer on the Evolving Basal Cell Carcinoma Landscape

**BASAL CELL CARCINOMA (BCC)** is one of the most common forms of cancer.<sup>1</sup> Although most cancer registries do not collect BCC data,<sup>2</sup> the most recent incidence study estimated that 3.3 million Americans had nonmelanoma skin cancers (NMSCs),<sup>3</sup> the majority of which are BCCs.<sup>1</sup> The estimated cost of treating NMSC in the United States is more than \$1.4 billion annually, making NMSC 1 of the top 5 most expensive cancers.<sup>4</sup> Additionally, the overall incidence of BCC continues to increase, which is likely because of improved detection, increased sun exposure, and longer life expectancy.<sup>5</sup> BCC occurs most frequently on the head and neck, particularly on the nose and eyelids, and men appear to be more commonly affected than women.<sup>6</sup>

Basal cell carcinoma can affect patients' activities of daily living, as well as their physical, psychosocial, and emotional health.<sup>7,8</sup> Patients may experience pain, stress, itching, red or bleeding lesions, trouble sleeping, or lack of energy.<sup>7</sup>

Although most cases of BCC are treatable, a smaller subset of BCCs can become advanced (either locally advanced or metastatic).<sup>9</sup> Advanced BCC, compared with noninvasive, nonmetastatic disease, has a poor prognosis.

This article provides an overview of the incidence, diagnosis, and treatment of BCC, including the evolving therapeutic spectrum for advanced BCCs.

## Incidence and Risk Factors

Basal cell carcinoma occurs most often in fair-skinned individuals. Other risk factors for BCC include history of sunburn, high cumulative UV exposure, and advanced age.<sup>10,11</sup> A personal history of skin cancer or compromised immune system can also increase risk, as can exposure to arsenic or ionizing radiation for treatment of skin diseases or childhood cancer.<sup>10,12</sup> Another recognized risk factor is indoor tanning. In a 2014 study, younger patients (aged 25 to 50 years) with a history of indoor tanning had an odds ratio for developing BCC of 1.6 (95% CI, 1.3-2.1) versus controls.<sup>13</sup> People who lightly tan or not at all after sun exposure have a lower risk of BCC when compared with those who tan regularly.<sup>14</sup>

In a 2015 study of patients with BCC diagnoses between 1998 and 2012, female patients 40 years and older and male patients 64 years and older had a higher incidence of BCC.<sup>4</sup> The incidence of BCC in other age groups was unchanged or slightly decreased.<sup>4</sup> However, increased incidence has been observed among younger age groups, as well.<sup>8</sup>

People who are immunosuppressed after organ transplantation have a 5 to 10 times greater risk for BCC than the general population.<sup>12</sup> Patients with HIV have an adjusted rate ratio of 2.1 (95% CI, 1.8-2.3) for developing BCC versus those without HIV.<sup>15</sup> Ionizing radiation, which has been used to treat malignancy and other conditions, is also a risk factor for developing BCC. Patients exposed to 35 Gy or more as children have an odds ratio of 39.8 (95% CI, 8.6-185) for developing BCC later in life.<sup>16</sup> Other conditions that have been linked to an increased risk of BCC include the genetic diseases xeroderma pigmentosum and Gorlin syndrome.<sup>17</sup>

## Histological Subtypes

Basal cell carcinoma is characterized by abnormally proliferative keratinocytes derived from the basal cell layer of the epidermis.<sup>18</sup> BCC is classified into various

pathohistological subtypes based on growth patterns. These subtypes include nodular, superficial, morpheaform, infiltrative, fibroepithelial, micronodular, and basosquamous (also known as metatypical or mixed BCC).<sup>10,18</sup>

Between 60% and 80% of all BCC is nodular.<sup>10</sup> Nodular BCC has a pearly or translucent appearance, sometimes with telangiectatic vessels, and it most often occurs on the head and neck. Ulceration may be present when tumors are large. Approximately 20% of BCC is superficial type and occurs on the trunk and limbs. It appears as well-circumscribed, scaly, red patches or plaques, and it may have central atrophy and a rolled border.<sup>10</sup>

Morpheaform-type carcinoma (also called sclerosing or desmoplastic type) makes up 5% to 10% of all BCC.<sup>10</sup> Morpheaform tumors are often found on the head and neck and are flesh-colored plaques with poorly defined borders. Infiltrative-type BCC usually occurs in the context of preexisting BCC of other types.<sup>10</sup> Clinically, these lesions are white or pale pink, poorly defined, indurated, and flat or depressed, and possibly have erosions or ulcerations.<sup>10</sup> Fibroepithelial-type BCC commonly occurs on the lower back as skin-colored or erythematous papules or papulonodular lesions.<sup>10</sup> Basal cell carcinomas with pigmentation can be seen in any subtype; these lesions are most often seen in patients of Asian or African descent and are rare in patients of Caucasian descent.<sup>10</sup>

Micronodular tumors, which present with smaller tumor nests, have a higher risk of subclinical extension than nodular BCCs.<sup>19</sup> However, such a classification has yet to be defined. In the interim, the currently most favored classification is one based predominantly on histological growth pattern. This classification contributes to the useful concept of low- and high-risk histological subtypes of BCC. The latter are characterized by an increased probability of subclinical extension and/or incomplete excision and/or aggressive local invasive behavior and/or local recurrence. The Royal College of Pathologists has published a minimum dataset for the histopathological reporting of BCC and this has been written to be compatible with the British Association of Dermatologists' management guidelines. Growth patterns to be reported include nodular, superficial, infiltrative/morpheic, and micronodular types. Basosquamous BCC has mixed histology with features of both basal cell and squamous cell cancer.<sup>12</sup> It appears that the risk for metastasis is related to the squamous component of the cancer, and it has a metastatic potential similar to that of pure squamous cancers.<sup>12</sup>

Morpheaform, infiltrative, and basosquamous types are more likely to be excised incompletely, recur, and metastasize.<sup>12,19,20</sup> For the more aggressive subtypes (ie, micronodular, morpheic, and infiltrative), it is more difficult to define borders clinically; as a result, these types are more often excised with incomplete margins.<sup>19</sup>

### Considerations for Treatment Decision-Making

Biopsy technique should be determined by the characteristics of the tumor. Morphological characteristics to consider include likely histologic subtype and depth, natural history, and anatomic location.<sup>1</sup> Patient-specific factors, such as bleeding, wound healing diatheses, and patient preference, should also be considered.<sup>1</sup> Punch or shave biopsies are usually able to detect the more aggressive histologic subtypes of BCC. Shave biopsy is likely to make the diagnosis but will not reliably assess depth.<sup>1</sup> Excisional biopsy will make the diagnosis and stage the tumor while providing definitive treatment in most cases.<sup>1</sup>

For nonadvanced disease, local treatment with excision or destruction of the tumor and a small margin of normal skin is usually curative.<sup>12</sup> However, in the small portion of BCC cases that are locally aggressive or metastatic, systemic therapy or radiation therapy may be appropriate first-line or adjuvant treatment.<sup>12</sup>

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**Though treatment of BCC is usually surgical, multidisciplinary evaluation is crucial to ensure optimal outcomes, especially in patients with advanced disease.**

Though treatment of BCC is usually surgical, multidisciplinary evaluation is crucial to ensure optimal outcomes, especially in patients with advanced disease. Depending on the details of an individual's tumor, the treatment team may include dermatologists, Mohs surgeons, surgical oncologists, medical oncologists, nurse practitioners, social workers, and nutrition specialists.<sup>9,21</sup> In a multidisciplinary evaluation, the stage of the cancer, tumor location, immune health, patient age, comorbidities, lifestyle factors, and risk of recurrence or spread are considered when selecting the approach.<sup>9</sup> Depending on the individual and their disease, treatment may include surgical excision, Mohs surgery, curettage and electrocauterization, cryotherapy, radiotherapy, photodynamic therapy, topical therapy, or systemic therapy.<sup>12</sup>

Surgical excision with adequate margin is the most common therapy, and it is the most effective therapy when it is complete.<sup>12</sup> For well-circumscribed BCC lesions less than 2 cm in diameter, excision with 4-mm clinical margins should completely excise the lesion in more than 95% of

cases.<sup>12</sup> BCC with high-risk features should have larger margins because of the increased likelihood of clinically occult local invasion. In cases with incomplete excision, reexcision is recommended; if reexcision is not possible, then radiation therapy may be appropriate.<sup>12</sup>

Mohs surgery involves iterative excision and microscopic examination of a tumor specimen until clear margins are obtained, ensuring complete excision while minimizing loss of uninvolved tissue.<sup>12,22</sup> Mohs surgery is best suited to areas such as the head and neck, where tissue coverage and cosmetic outcomes are a concern, or in large morphoeic or recurrent lesions when more aggressive tumor infiltration of surrounding tissue is likely.<sup>22</sup> The 5-year recurrence rate for primary lesions is 1%, and it is 5.6% for recurrent lesions.<sup>12</sup>

Curettage and electrosurgery use electrosurgical devices to ablate the tumor with 5-year cure in 92% of patients. This procedure, however, precludes margin assessment and should be used only for low-risk lesions. It should also be avoided in the head and neck region.<sup>10</sup>

Cryotherapy uses liquid nitrogen or frozen carbon dioxide to destroy tumor tissue and is best used in low-risk lesions.<sup>12</sup> Ideally, the lesion should be biopsied prior to treatment to rule out more aggressive tumor types. According to retrospective reviews, 5-year recurrence is seen in up to 13% of cases, but in prospective trials, recurrence has been as high as 39%.<sup>10,12</sup> Cryotherapy outcomes may vary in part because no standard protocol exists regarding the number and duration of freeze-thaw cycles. Another factor to consider with cryotherapy is that it can potentially result in permanent hypopigmentation, and margins cannot be assessed.<sup>10,23</sup>

Radiotherapy is appropriate for patients for whom surgical excision is inappropriate because of comorbidity, extensive local invasion, or patient preference.<sup>1</sup> In some reviews, long-term cure rates are reported to be 93% to 96%.<sup>12</sup> However, in a prospective randomized study of surgery versus radiotherapy as primary treatment, radiation therapy was associated with a higher recurrence rate (7.5% vs 0.7%;  $P = .003$ ), worse cosmetic result, and more complications.<sup>12</sup>

Finally, topical treatments such as 5% imiquimod or 5-fluorouracil can be used to treat multiple low-risk lesions. In one phase 3 trial, there were no signs of recurrence 3 years after imiquimod treatment in 84% of patients.<sup>12</sup> Surgical treatment was 98% successful in this study ( $P < .001$ ), but imiquimod provided better cosmetic outcomes.<sup>12</sup> 5-fluorouracil has similar outcomes based on limited literature.<sup>12</sup>

### Recurring and Advanced BCC

Although most BCC cases are unlikely to shorten life, metastasize, invade deeply into tissues, or recur, a small

percentage become locally advanced or metastasize and become a significant burden for patients.<sup>7,8,18</sup> Of recurrent cases, 90% are in the head and neck, and the rate of recurrence increases with tumor size and location on the face.<sup>18</sup> As much as 65% of recurrent tumors have aggressive histological features, and such tumors tend to recur without early symptoms, which can delay diagnosis and treatment.<sup>18</sup>

Larger lesions can penetrate deeply into the skin or surrounding tissue, destroying tissue and forming difficult-to-treat, locally advanced disease. Multiple factors are associated with locally advanced BCC, including tumor size, location in the mask area of the face, presence of multiple lesions, aggressive histology, and likelihood of incomplete treatment of the disease (eg, with recurrent tumors).<sup>9</sup>

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**Patients with advanced BCC likely have significant personal burdens associated with disease and treatment. These can include pain, blood loss, anemia and fatigue, open wounds, and limitations in function due to tumor location.**

Metastatic basal cell cancer is rare, occurring in less than 1% of cases.<sup>22</sup> Risk factors for occult metastatic disease include a tumor diameter less than 2 cm, location on the central part of the face or ears, long-standing presence of the lesion, incomplete excision, aggressive histologic pattern, and perineural or perivascular involvement.<sup>18,22</sup> Basal cell carcinoma most often spreads to regional lymph nodes, but bone, lung, and liver metastasis can occur less commonly.<sup>1,18</sup> Metastatic BCC can involve large areas of soft tissue, cartilage, and bone, and it can lead to substantial disfigurement.<sup>20,24,25</sup> Metastatic BCC has historically been associated with a very poor prognosis: There are few treatment options, and the mean survival ranges from 8 months to 3.6 years.<sup>1,22</sup>

Patients with advanced BCC likely have significant personal burdens associated with disease and treatment. These can include pain, blood loss, anemia and fatigue, open wounds, and limitations in function due to tumor location. Patients may also experience adverse effects from surgery, radiation, or chemotherapy.<sup>7,8</sup>

Guidelines for treatment for advanced BCCs are lacking, and treatment strategies vary widely.<sup>20</sup> Complete excision with negative margins can be effective, but aggressive surgery may be disfiguring or impair function.<sup>24</sup> In some cases, radiotherapy is used to treat patients who are not surgical candidates; it may also be used as adjuvant therapy in patients who have incomplete resections.<sup>10</sup> Systemic chemotherapy has been used to treat advanced disease, but no standard regimen exists, and response to traditional chemotherapy in advanced BCC has been limited.<sup>9</sup>

Recently developed medications are changing the treatment landscape for advanced BCC.<sup>12</sup> Several Hedgehog pathway inhibitors have been developed and show promise in clinical trials.<sup>12,24</sup> During embryogenesis, Hedgehog signaling guides differentiation, proliferation, and tissue patterning.<sup>9</sup> In adults, Hedgehog signaling maintains stem cells and certain tissues.<sup>9</sup> Hedgehog mutations are found in most BCC tumors and are thought to lead to the cancer phenotype. This led researchers to investigate Hedgehog pathway inhibitors for efficacy in BCC.<sup>9</sup>

Vismodegib is a Hedgehog pathway inhibitor that showed efficacy in metastatic and locally advanced BCC. In a 2012 phase 2 study of patients with advanced BCC, for whom surgery was inappropriate, the response rate was 30% (95% CI, 16%-48%;  $P = .001$ ) in the 33 patients with metastatic BCC, and 43% (95% CI, 31%-56%;  $P < .001$ ) in the 63 patients with locally advanced BCC.<sup>26</sup> There were complete responses in 21% of patients.<sup>26</sup> Response to treatment lasted for a median of 7.6 months.<sup>26</sup> More than 30% of patients experienced muscle spasms, alopecia, disturbance in taste, or weight loss and/or fatigue.<sup>26</sup> Seven deaths occurred because of adverse events.<sup>26</sup>

Another Hedgehog pathway inhibitor, sonidegib, was studied in 230 patients at 2 different doses. At 13.9 months, 36% of patients (20 of 55 patients) receiving 200 mg of sonidegib had a response (95% CI, 24%-50%), and 34% of patients (39 of 116 patients) receiving 800 mg of sonidegib had a response (95% CI, 25%-43%).<sup>24</sup> Serious adverse events occurred in 14% of patients (11 of 79 patients) in the 200-mg group and in 30% of patients (45 of 150 patients) in the 800-mg group.<sup>24</sup> Several other Hedgehog pathway inhibitors are under investigation.<sup>27</sup>

In addition to Hedgehog pathway inhibitors, the BCC treatment spectrum now also encompasses immunotherapy. Cemiplimab-rwlc is a monoclonal antibody that inhibits PD-1 activity.<sup>28</sup> In 2021, the FDA approved cemiplimab-rwlc for patients with locally advanced BCC previously treated with a Hedgehog pathway inhibitor or for patients with locally advanced BCC for whom a Hedgehog pathway inhibitor is inappropriate.<sup>28</sup> It was also approved for patients with metastatic BCC previously treated with a Hedgehog pathway inhibitor or for patients

with metastatic BCC for whom a Hedgehog pathway inhibitor is inappropriate.<sup>28</sup>

Given the challenges of treating advanced BCCs, the addition of options with new mechanisms may provide new ways of optimizing care and improving outcomes. ♦

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# Recent Developments in the Treatment of Advanced Basal Cell Carcinoma

**ALTHOUGH RELATIVELY SMALL IN NUMBER**, advanced basal cell carcinoma (BCC) cases often resist standard BCC therapy and require other types of treatment.<sup>1</sup> Treating locally advanced BCC (laBCC) or metastatic BCC (mBCC) may involve a variety of treatment modalities, including surgery—standard excision, electrodesiccation and curettage, Mohs micrographic surgery, and/or resection with complete circumferential peripheral and deep margin assessment—radiation therapy (RT), targeted treatment with a Hedgehog pathway inhibitor (HHI), systemic immunotherapies, and/or participation in a clinical trial.<sup>2,3</sup> Therefore, the involvement of surgical oncologists, radiation oncologists, and medical oncologists who specialize in each of these areas is key to achieving optimal outcomes for patients.<sup>4</sup>

When topical therapy, surgery, or RT is unlikely to be curative for recurrent or advanced BCC disease, systemic therapy may be considered.<sup>2</sup> If systemic treatment is to be used, HHIs should be considered.<sup>2</sup> Notably, HHIs are associated with an adverse event (AE) profile that results in treatment discontinuation in up to 30% of patients.<sup>4</sup> In these cases, the multidisciplinary care team may consider dosage alterations and supportive care.<sup>4</sup> For the many patients who initially experience a complete clinical response on an HHI but eventually become intolerant or experience tumor regrowth, second-line therapies such as immune checkpoint inhibitors (ICIs) may be considered.<sup>3,5</sup>

This article reviews the pathophysiology of advanced BCC and explores treatment options, focusing on HHIs and ICIs.

## HHIs as First-Line Therapy

The HH signaling pathway is involved in the proper maintenance, renewal, and regeneration of tissues.<sup>3,6</sup> Abnormal HH activity plays a role in the growth of many types of cancer.<sup>7</sup> Relevant to BCC is that a gene known as *PTCH1* codes for the HH receptor.<sup>6,8</sup> Under normal circumstances, the PTCH1 protein coded by the *PTCH1* gene inhibits the signaling activity of SMO, a transmembrane oncogenic protein.<sup>4,8</sup> The SMO protein, in turn, signals for DNA replication within basal cells.<sup>6,8</sup>

The *PTCH1* gene is highly susceptible to UV-induced damage from the sun's rays.<sup>6</sup> Mutated *PTCH1* genes create versions of the PTCH1 protein that do not properly inhibit the SMO protein; this leaves the SMO in a constant state of activation, which leads to uncontrolled proliferation of basal cells.<sup>6,8</sup> Aberrant activation of the HH signaling pathway, through a mutated *PTCH1* gene or a mutated

*SMO* gene, is responsible for nearly all cases of sporadic BCC, accounting for 85% and 10% of cases, respectively.<sup>3,9</sup>

HHIs are small molecules that restrain some element of the HH signaling pathway. Unlike traditional chemotherapy, which affects a wide range of cells, HHIs target specific molecules.<sup>1</sup> Although HHIs targeting other components of the HH signaling pathway are being studied and have been developed for other cancers, those for advanced BCC have largely focused on inhibiting the SMO protein.<sup>3</sup> The 2 HHIs currently approved for use in the advanced BCC setting are vismodegib and sonidegib.<sup>3,8,9</sup>

Vismodegib is approved for use in either laBCC or mBCC<sup>10</sup>; sonidegib currently has an indication for laBCC only.<sup>11</sup> ERIVANCE (NCT00833417)<sup>8</sup> and BOLT (NCT01327053)<sup>9</sup> were the phase 2 trials that established the safety and efficacy of vismodegib and sonidegib in the advanced BCC setting, respectively.<sup>3,4,8,9</sup>

## Vismodegib

The HHI vismodegib is a small molecule inhibitor of SMO.<sup>3,8</sup> In ERIVANCE, the 96 patients (33 with mBCC and 63 with laBCC) who were ultimately included in the efficacy analysis were given 150 mg vismodegib once daily.<sup>8</sup> The trial's primary end point, as assessed by an independent review committee (IRC), was objective response rate (ORR).<sup>8</sup> At the study's data cutoff point—which came after a median duration of drug exposure of 10 months in the mBCC group and 9.7 months in the laBCC group<sup>8</sup>—ORR was experienced by 30% and 43% of patients, respectively.<sup>8</sup> This was significantly higher than the predicted 10% ( $P = .001$ ) and 20% ( $P < .001$ ), respectively, expected for the null hypothesis in both groups.<sup>8</sup>

The safety analyses included 104 patients (33 with mBCC and 71 with laBCC).<sup>8</sup> At the same data cutoff point and after the same median duration of drug exposure of approximately 10 months in both groups, the most common AE of any grade across both cohorts of patients included muscle spasms (68%), alopecia (63%), dysgeusia (51%), weight loss (46%), asthenia (36%), nausea (29%), loss of appetite (23%), and diarrhea (22%).<sup>8</sup>

Twelve percent (12%) experienced an AE leading to discontinuation of vismodegib; the most common reason was muscle spasms.<sup>8</sup>

## Sonidegib

Sonidegib is also a small molecule SMO antagonist.<sup>3,9</sup> In the BOLT trial, the 171 patients (36 with mBCC and 135

with laBCC) who were ultimately included in the efficacy analysis were randomized 1:2 to receive sonidegib 200 mg once daily (55 patients) or 800 mg once daily (116 patients).<sup>9</sup> As in ERIVANCE, the primary end point in BOLT, as assessed by an IRC, was ORR.<sup>9</sup> The median follow-up time among all patients included in the trial was 13.9 months.<sup>9</sup> At follow-up, objective response in the 200-mg cohort was experienced by 15% of patients with mBCC and 47% of patients with laBCC, as well as by 17% of patients with mBCC and 35% of patients with laBCC in the 800-mg cohort.<sup>9</sup>

The safety analysis included 79 patients in the 200-mg dose cohort and 150 patients in the 800-mg dose cohort.<sup>9</sup> After a median duration of drug exposure of 8.9 months in the 200-mg cohort and 6.5 months in the 800-mg cohort, there were numerically lower proportions of patients who experienced AEs of any grade in the 200-mg cohort than in the 800-mg cohort.<sup>9</sup> The most common AEs were muscle spasms (49% [200-mg cohort] and 67% [800-mg cohort]), alopecia (43% and 55%), dysgeusia (38% and 59%), nausea (33% and 45%), increased serum creatinine (29% and 36%), fatigue (29% and 36%), weight loss (27% and 38%), and diarrhea (24% and 22%).<sup>9</sup> Loss of appetite and myalgias were also commonly experienced in the 800-mg cohort.<sup>9</sup>

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**For reasons of efficacy, QOL, and overall disease-management costs, patients who progress on HHI therapy or still cannot tolerate the AEs often require a second-line option.**

The rate of study drug discontinuation due to AEs was numerically lower in the 200-mg dose cohort compared with the 800-mg dose cohort (22% vs 36%, respectively), and the most common reason for study drug discontinuation in either cohort was muscle spasms.<sup>9</sup> A numerically higher proportion of patients in the 200-mg dose group vs the 800-mg dose group were able to remain on therapy for 4 months or longer (91% vs 70%, respectively).<sup>9</sup>

The study investigators concluded that because anti-tumor activity was observed in both dose cohorts but the lower dose was associated with a more favorable AE profile, the 200-mg dose of sonidegib should be suggested for patients with advanced BCC.<sup>9</sup>

## AE Mitigation Strategies and Ongoing HHI Challenges

The safety profile of HHIs is notable, with results from the ERIVANCE and BOLT trials indicating that AEs lead to treatment discontinuation in up to 30% of patients.<sup>4</sup> Muscle spasms, dysgeusia, alopecia, asthenia, and weight loss are common among the HHIs as a class and are experienced by the majority of patients.<sup>4,12</sup> In addition, vismodegib and sonidegib have a moderate to high emetogenic potential (ie, causes nausea and vomiting).<sup>12</sup>

Strategies utilized to attenuate toxicities and improve drug tolerability and quality of life (QOL) include intermittent dosing schedules (treatment interruptions [drug holidays] or every-other-day dosing), dose reductions, and/or supportive care with pharmacological agents.<sup>3,4,12</sup>

Calcium channel blockers (eg, amlodipine, diltiazem, or verapamil), nerve stabilizers (eg, gabapentin, pregabalin), muscle relaxers (eg, cyclobenzaprine), lidocaine, levetiracetam, and vitamin B complex have demonstrated effectiveness in treating HHI-induced muscle spasms of grade 1/2.<sup>12</sup> For muscle spasms of grade 3 and higher, a treatment interruption for at least 2 cycles or changing to a 1-week-on/1-week-off dosing regimen have proved to be helpful.<sup>12</sup>

A variety of dietary modifications (eg, adding spice, lemons, or sweeteners) can be recommended to help mitigate the taste dampening associated with HHIs.<sup>12</sup> A dose interruption of at least 4 weeks is usually required for taste sensation to normalize, considering the half-life of HHIs and the life span of taste cells (10-24 days).<sup>12</sup>

Use of minoxidil and dihydrotestosterone inhibitors (eg, spironolactone, finasteride) can be recommended for HHI-induced alopecia.<sup>12</sup> However, it is important for patients to understand that the HHI-induced alopecia is different in nature from chemotherapy-induced alopecia, in that it develops gradually, could be delayed, and can occur after HHI therapy is stopped.<sup>12</sup>

Use of levocarnitine and delta-9-tetrahydrocannabinol (ie, medical marijuana) may also be useful for treating muscle spasms and taste disturbances associated with HHI therapy, respectively.<sup>12</sup>

Although the adjunctive care used to mitigate HHI AEs can increase patient QOL,<sup>4</sup> some challenges remain regarding tolerability and safety. For example, some patients who initially experience a complete clinical response on an HHI eventually experience tumor regrowth,<sup>3,5</sup> making the optimal duration of treatment hard to define and overall treatment costs hard to predict. Other patients become intolerant to HHI therapy.<sup>3,5</sup> On account of regrowth or intolerance, many patients discontinue treatment entirely.<sup>5,8,9</sup> For instance, in the final analysis of the ERIVANCE trial, which included 39 months of follow-up data, only 8 of 104 patients (7.7%) were continuing to

receive treatment with vismodegib per protocol, whereas the vast majority (n = 96; 92.3%) had discontinued treatment. The most common reasons for discontinuation were AEs (21.2%) or disease progression (27.9%).<sup>5</sup>

### ICIs and Emerging Options in Treating Advanced BCC

For reasons of efficacy, QOL, and overall disease-management costs, patients who progress on HHI therapy or still cannot tolerate the AEs often require a second-line option. In February 2021, the ICI cemiplimab was approved by the FDA for use in patients with laBCC who have been previously treated with an HHI or for whom an HHI is not appropriate.<sup>13,14</sup> Prior to this approval, patients with laBCC had no approved therapeutic option beyond first-line treatment with an HHI.<sup>14</sup> The FDA placed cemiplimab under accelerated approval for use in mBCC as well. Other HHIs, other ICIs, and the antifungal agent itraconazole are also being investigated to treat advanced BCC.

#### Cemiplimab

Cemiplimab gained its first US approval in 2018 for use in locally advanced or metastatic cutaneous squamous cell carcinoma. Like other ICIs, and unlike HHIs, cemiplimab seeks to restimulate the immune system after cancer has suppressed it and to promote T-cell activity and cancer surveillance.<sup>13,15-18</sup> Cemiplimab targets PD-L1 and helps prevent PD-L1 from binding to and activating the PD-1 receptor on the surface of T cells. Therefore, this fully human monoclonal antibody (mAb) blocks cancer cells from suppressing T-cell activation.<sup>13,15,19</sup>

The approval of cemiplimab was based on the results of Study 1620 (NCT03132636), an open-label, multicenter, nonrandomized, single-arm phase 2 study.<sup>13,14</sup> In the trial, investigators evaluated the efficacy and safety of cemiplimab 350 mg every 3 weeks in patients with laBCC or mBCC who had previously been treated with an HHI.<sup>13,14</sup> Patients who had progressed on, failed (did not achieve an objective response after 9 months), or were intolerant to HHI therapy were included in the trial.<sup>13,14</sup> In addition, patients had to be ineligible for curative surgery or curative RT.<sup>14</sup> The primary efficacy end point was ORR, as assessed by IRC.<sup>14</sup>

The Study 1620 results are shown in the **Table**.<sup>13,14</sup> Among the efficacy population (n = 121), the ORRs were 29% and 21% for the laBCC and mBCC cohorts, respectively.<sup>13,14</sup>

After a median duration of cemiplimab exposure of 42 weeks in the safety population (n = 132),<sup>13</sup> the most common AEs of any grade were fatigue (49%), musculoskeletal pain (33%), diarrhea (25%), rash (22%), pruritus (20%), and upper respiratory tract infection (15%).<sup>13</sup> Discontinuation of cemiplimab during the trial because of AEs occurred in 13% of patients, with the

**TABLE.** Efficacy Results for NCT03132636 (phase 2 trial of cemiplimab in advanced BCC)<sup>13,14</sup>

Efficacy end point	laBCC (n = 84) n (%)	mBCC (n = 28) n (%)
<b>Primary efficacy end point</b>		
ORR	24 (29%)	6 (21%)
<b>Secondary efficacy end points</b>		
CR	5 (6%)	0 (0%)
PR	19 (23%)	6 (21%)
DOR (median, months)	NR	NR
Patients with observed DOR > 6 months	19 (79%)	6 (21%)

BCC, basal cell carcinoma; CR, complete response; DOR, duration of response; laBCC, locally advanced BCC; mBCC, metastatic BCC; NR, not reached; ORR, objective response rate; PR, partial response.

most common reasons being colitis and overall physical health deterioration.<sup>13</sup>

Study 1620 demonstrated the efficacy of cemiplimab in treating laBCC in patients who had previously received HHI therapy.<sup>14</sup> Cemiplimab shows promise for the many patients who discontinue HHI therapy because of toxicity or disease progression.<sup>14</sup> Moreover, it ushers in the entire ICI class and opens a new horizon for advanced BCC therapy.

#### Investigational Agents

Beyond the approval of cemiplimab, the horizon for immune approaches to advanced BCC appears promising. Several HHIs—glasdegib (PF-04449913), taladegib (LY2940680), BMS-833923—along with the antifungal agent itraconazole are being researched as advanced BCC therapies.<sup>3,6,20</sup> Moreover, certain ICIs that have been approved for use in other cancers are being investigated for use in BCC. These include pembrolizumab<sup>16,17</sup> and nivolumab with or without ipilimumab.<sup>18,19,21</sup> Like cemiplimab, pembrolizumab and nivolumab are both mAbs that block the PD-1 receptor on T cells.<sup>17,18</sup> Ipilimumab is a mAb that binds to CTLA-4, an inhibitor of T-cell activity.<sup>21</sup> Blockade of CTLA-4 allows effector T cells to activate, proliferate, and infiltrate tumors instead of remaining in a quiescent state.<sup>21</sup>

Pembrolizumab is being studied for advanced BCC treatment both as a monotherapy and in combination with an HHI. In a proof-of-principle, nonrandomized, open-label study (N = 16) of pembrolizumab with or without vismodegib given to patients with advanced BCC, the ORR was 38% at 18 weeks (44% for the pembrolizumab monotherapy group and 29% for the dual-therapy group).<sup>19</sup> Among the 6 patients who demonstrated a response, the median duration of response (DOR) was 67.3 weeks.<sup>19</sup>

Progression-free survival (PFS) and overall survival (OS) at 1 year were 70% and 94%, respectively.<sup>19</sup> Of a total of 98 AEs observed (any grade), none were life-threatening, and only 3 were considered severe (grade 3).<sup>19</sup>

Nivolumab with or without ipilimumab is being studied for use in laBCC and mBCC in an ongoing phase 2 open-label trial (NCT03521830).<sup>22</sup> Nivolumab monotherapy is being given to patients who are PD-1 inhibitor naive and have unresectable disease previously treated with 2 or fewer prior systemic therapies (cohort A).<sup>22</sup> Nivolumab plus ipilimumab dual therapy is being given to patients with disease progression after being on PD-1 inhibitor therapy (cohort B).<sup>22</sup> The primary outcome measure is ORR; secondary outcome measures are PFS, DOR, and OS.<sup>22</sup>

## Conclusions

Given the challenges of treating advanced BCCs, the approval of a new class of agents coupled with a robust pipeline suggests the potential for improved outcomes for patients. With more avenues for interventions and a continued emphasis on multidisciplinary approaches, healthcare professionals may also learn more about the risks and likelihoods of BCCs becoming advanced and identify appropriate treatments for the optimization of patient care. ♦

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# Carving Out the Role of Immunotherapy in the Treatment of Basal Cell Carcinoma

Q&A With Omid Hamid, MD



## OMID HAMID, MD

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**AJMC®:** Among patients with more advanced cases of basal cell carcinoma (BCC), how do you identify those at high-risk for disease progression or intolerance when it comes to the use of Hedgehog inhibitors?

**HAMID:** There are multiple ways of identifying patients with basal cell carcinoma with high recurrence risk. They are clearly delineated in multiple different publications and categories, but I would say, per the National Comprehensive Cancer Network, those at high risk have locations that are on the cheeks, forehead, scalp, neck, or periorbital area. Otherwise, if the lesions are on the trunk and extremities, they're greater than 2 cm. We often talk about the mask area of the face and the central eyelids and eyebrows in the periorbital area where the borders are poorly defined. Here, recurrent BCC is high risk.

Then, of course, we talk about the population of patients with significant risk [for] any type of nonmelanomatous skin cancer. These are patients with prior immunosuppression, whether they're on immunosuppressive agents for a connective tissue or autoimmune disease, if they have CLL [chronic lymphocytic leukemia], or if they have some other form of immunosuppression.

Sites of prior radiation or prior surgery and recurrence are also high risk. There are subtypes that are low risk: nodular and superficial. There are also subtypes that are high risk, which are those with an aggressive growth pattern.

**AJMC®:** What factors affect treatment sequencing for patients with locally advanced and metastatic BCC?

**HAMID:** The treatment algorithm is important here for patients with high-risk disease. You need to [determine] if surgery is possible, and then you need to look at greater margins. If it's not surgery, then it's radiation. Then, for someone for whom surgery is not feasible, [or] those who refuse surgery, or [in] whom there's evidence of locally advanced or metastatic disease, it's important to bring in an interdisciplinary tumor board like we do here at The Angeles Clinic to take care of patients with BCC.

Clearly, [choosing] which therapy would be appropriate is important, as is how to discuss this with the patient. The modalities that have been utilized to treat patients are mostly surgery radiation excision, and curettage and excision. With recurrent BCC, the risk of recurrence is greater. The standard for a patient with primary BCC should be surgery with Mohs therapy, and if that is not possible, then the decision is surgical excision vs radiation.

**AJMC®:** What factors do you consider when a patient with BCC moves beyond their initial treatment? What influences your therapeutic decision-making in that second-line setting?

**HAMID:** The first thing to know in primary BCC is that there are huge discussions about what you would utilize as an appropriate therapy; that requires an understanding of the role of the therapy initially as well as the functionality and cosmesis of the area. You clearly have areas that are high risk, but these are also significant for loss of function, in an area like the eyelid. If you have a cosmetic

outcome that is deformative, or if you have fibrosis from radiation, there is morbidity. The goal at this time is the ability to support the patient in the best way possible.

In recurrent disease, you need to have an extensive discussion about whether returning to surgical or radiation modalities is appropriate because the tumor history has told you that you will be back where you are again. [That's when] we start discussing the application of Hedgehog inhibitors or other therapeutic agents to prevent recurrence, or they are used in a neoadjuvant fashion. That's a setting that's currently in flux, but it is important. Before we had Hedgehog inhibitors in the setting of multiple recurrences, the only options were disfiguring surgeries. One of the greatest aspects of being involved in the development of Hedgehog inhibitors is the ability to avoid the severe morbidity from surgery.

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**“We now have significant therapies that are giving us a road map on how to take care of each patient. Clearly, we’ve been reintroduced to the role of surgery and radiation as adjuncts to Hedgehog inhibitors and immunotherapies.”**

**AJMC®: What is your experience with tolerability concerns with Hedgehog inhibitors? What types of adjunctive care and monitoring do you use for patients who experience adverse events?**

**HAMID:** There is another side of Hedgehog pathway inhibitors: the adverse events that are significant. These include alopecia; muscle spasms, which are cramps that are unrelated to anything that you can manipulate with electrolytes; and weight loss from increased glucose uptake but also from dysgeusia and ageusia. Dysgeusia is a change in taste, and ageusia is a loss of taste. It's not that you're nauseous or vomiting; it's that the taste is different. Patients talk about a metallic taste in their mouths such that they don't have the desire to eat, or they don't get that same type of benefit and satisfaction from eating. There are also some cardiac concerns. For these patients, managing adverse events leads to discussions about minoxidil for the hair

loss, nutrition consultation, or hydration and stretching for the muscle spasms. These are clearly important for patients, as the majority of them are older, when recovering from a significant morbidity is harder.

**AJMC®: What is immunotherapy's role in patients with recurrent BCC? What factors would you consider when selecting a Hedgehog inhibitor vs immunotherapy?**

**HAMID:** The current approval for immunotherapy is in consideration for treatment after failure and progression on a Hedgehog inhibitor, but it also entails this idea of intolerance to a Hedgehog inhibitor. I think that's where we spend the majority of our time talking about the appropriate first-line therapy. Obviously, with these approvals, we will look at first-line immunotherapy and the benefits vs Hedgehog inhibitors. Those data are coming forward.

In immunotherapy, which is my sphere of research, we've known that BCCs have high mutational burdens—meaning they have a high level of neoantigens, which are proteins that stimulate the immune system. Just as we've known that in melanoma, we've known that in Merkel cell carcinoma, and we've known that in cutaneous cell carcinoma. It made scientific sense to look at immunotherapies and the PD-1 inhibitors, more importantly, in these patients. We have seen the ability to have a significant response rate and the ability to have durable and deep responses with significant progression-free survival and duration of response.

We have now brought something else to our armamentarium. I was involved in some of the phase 1 and phase 2 work with Hedgehog inhibitors and have been intimately involved with checkpoint inhibitors. I can tell you that they both have different toxicity profiles that you need to look at when you discuss this with patients. You have the ability and time to evaluate both, and you also have the time to utilize immunotherapy. When we talk about immunotherapy, we talk about the need for a runway of time for the immune system to get activated. Most BCCs have slow growth kinetics; therefore, you have the ability to utilize them.

**AJMC®: How do you envision the future of care in BCC? Will any ongoing clinical trials in this sphere have an impact on the overall treatment landscape?**

**HAMID:** The future of care for BCC will include our evaluation of combinations of these therapies. There are trials of pembrolizumab and vismodegib for advanced BCCs that have been published, presented, and updated. There will likely be randomized trials for the first-line setting. Then of course, as we have learned about the utilization of combination immunotherapies, I would recommend for anyone involved to look at phase 1 trials studying combinations of immune therapies because they're everywhere. This is

where I would ask patients to go. The focal utilization of radiotherapy to stimulate an immune response is a paradigm that has garnered significant import in other solid tumors and will do so for patients with a BCC, as these can metastasize to lymph nodes and bone.

There's never been a more promising time [to treat BCC]. As I look back on my experience with patients with locally advanced and metastatic BCC and understand what they had to go through, all we had were radiation and surgical procedures. Now 2 pillars have been added to the care paradigm: targeted therapy with Hedgehog inhibitors and immunotherapy with PD-1 inhibitors, which not only have the ability to control disease, but they are also manageable.

**AJMC®: What patient- or treatment-related factors most influence your strategy for the overall management of patients with advanced BCC? Do you have any advice for clinicians to best optimize their approach to treatment for these patients?**

**HAMID:** I would say that this is like any other situation: Trying to classify a single patient among the group is difficult. The toxicity spectrum needs to be evaluated in addition to the efficacy that we can get from these drugs. It's a paradigm that's in flux. The best way to improve outcomes for patients is to utilize a multidisciplinary team approach to care, which includes supportive care, palliative care, and nursing. Also, the pathologist is very important, as is the surgical oncologist, the radiation oncologist, and the medical oncologist—and of course, the most important person is the patient.

As far as we have come, [we have] become more intricate in our care of patients, given our options and the benefits that we've seen. Years ago, when a basal cell carcinoma was recurrent, we were without options. We now have significant therapies that are giving us a road map on how to take care of each patient. Clearly, we've been reintroduced to the role of surgery and radiation as adjuncts to Hedgehog inhibitors and immunotherapies. ♦

# Optimizing Treatment for Advanced Basal Cell Carcinoma

Q&A With Todd Schlesinger, MD



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**AJMC®:** How do you assess whether a basal cell carcinoma (BCC) has potential to become advanced? At the point of diagnosis, what treatment options do you consider?

**SCHLESINGER:** There are certain things that we look at when it comes to whether a BCC is more advanced. One question is: Is the tumor of a large size? Another is: Is the tumor in an area that is close to a critical structure of the body? Is it near the eye? Will the removal of that tumor cause significant morbidity to the patient? Tumors may involve removing part of a nose, part of an ear, or another structure. Large or more advanced-appearing tumors may be ulcerated or show advanced features. BCCs that are recurrent and have been treated before with surgery, radiation, or possibly even other chemotherapeutic agents are more advanced and riskier. Other tumors display advanced features that may only be detected during removal, such as perineural invasion: Involving a nerve, especially a main nerve or a nerve greater than 0.1 mm, also increases the risk of the BCC.

We also think about tumor types histologically. Tumors of the morpheaform or sclerosing BCC pattern as seen under the microscope—and ulcerated BCC—are [riskier] because their growth pattern is not uniform; they may invade tissue in ways that are harder to detect. Collision tumors are those in which you have a squamous cell carcinoma and BCC in the same specimen. Those are also higher risk for progression: local spread and/or in transit metastasis, which is local lymphatic spread. Basal cell carcinomas spread locally most of the time. They usually spread by invading the tissue surrounding the tumor, but have potential for metastases as well.

Those are the first things you think of when you look at a tumor and you want to decide if it's advanced. You think about those risk factors. You also consider if a patient might be immunocompromised. Do they have factors that may allow that tumor to grow more quickly? Those are all first considerations that you would think about. But often, you first consider location, size, and the risk of surgery: What would happen to that patient if you were to remove the tumor with standard technique Mohs surgery or extirpation of any kind?

**AJMC®:** What is the importance of multidisciplinary care in treating of BCC?

**SCHLESINGER:** The multidisciplinary team, or MDT, is an important part of the care, and the patient is at its center. Depending on the tumor and its level of advancement, different team members may be involved. There is a major decision to be made between surgery and chemotherapy or surgery and radiation or [other options]. You may want to involve other specialties. If you're a dermatologist, that may [include] Mohs surgery, maybe medical oncology, surgical oncology, radiation oncology. It may be general surgery or head and neck oncology or head and neck surgery. A pathologist may also be involved.

The MDT is important because when these tumors become large or more advanced, you do run into additional risk factors that one specialty may not be able to manage. There could be a structural risk factor. Maybe there is an ophthalmological concern with an eye or an ear, nose, and throat concern with

an advanced tumor of the ear canal. Maybe neurology or neurosurgery should be involved. I think it's in the patient's best interest that they receive a multidisciplinary specialty approach. This is common in major academic centers, but an MDT may be hard to put together within a community physician group. Nevertheless, the patient should have the benefit of the different groups and opinions throughout their care and treatment.

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**“The multidisciplinary team is important because when these tumors become large or more advanced, you do run into additional risk factors that one specialty may not be able to manage.”**

**AJMC®: When do you decide that you need an MDT or another physician?**

**SCHLESINGER:** When a patient's tumor is at a point at which you think curative surgery or curative radiation is not possible, or if it's something you either can't treat yourself or [you] refer to a single place to be treated, you look into other options. In the community, MDT formation is often very loosely organized. There may be a text message or a phone call between yourself and another physician. There may be referral to another physician to take over the patient's care and use another team. Or it may be that you refer to different physicians and you manage that patient's care throughout the whole process. It looks different to different people and is based on the community you're in, who you're comfortable working with, and who you have available. Some people don't have all these physicians available. They have to refer to a major city or academic center and maybe into an existing MDT. However, if they're in a robust private medical care community, they may be able to put together an MDT and be its leader.

Communication becomes an issue with [the need to] pass around records and notes and information about the patient with their privacy in mind. But in private practice, MDT formation often starts with a phone call or text message to another doctor to get their opinion about what's going on and then maybe have the patient seen. Also, many of the major academic centers where we train have multidisciplinary tumor boards where those

patients are presented on a regular basis to a group. Some academic centers engage us community practitioners in grand rounds. If there is a local academic center that you're affiliated with, sometimes turning a patient into the grand rounds as a first step gets exposure to multiple specialties at once. Some opinions come out and you can then have multidisciplinary care.

**AJMC®: What role do Hedgehog inhibitors (HHIs) and immune checkpoint inhibitors (ICIs) have in the treatment of BCC? How do adverse effects (AEs) factor in?**

**SCHLESINGER:** It's exciting to have these new technologies available to our patients. ICIs pick up where Hedgehog pathways leave off. HHIs are great [for treating] patients with large tumors, multiple tumors, and some very advanced tumors. However, they require long-term treatment, and we don't really know what the end point is. They have their AEs, which are [often] manageable with dose modification and/or additional treatments.

Checkpoint inhibition is another excellent modality. It is also very powerful. It's a different mechanism of action: We're activating the patient's immune system to target tumors, to “uncloak” them so they can be seen by the circulating T cells and create a cytotoxic response within and around the tumor to help destroy it. ICIs take [efficacy] to another level. However, with ICIs, you have a greater depth and breadth of AEs that can occur. AEs are very common with ICIs, though most of the time not severe. We notice that ICI AEs can affect almost any organ system in the body, whereas HHI AEs are quite limited to gastrointestinal and neurological systems. HHIs can have other AEs, but because HHIs are focused on the Hedgehog pathway mutations that are occurring within the tumor itself, the AEs are limited to certain body systems. Because ICIs activate the body's immune system generally as well as at the tumor site, you can have a greater depth and breadth of AEs. You're a little more likely to have a more severe event with an ICI, but you're also able to treat tumors that are more advanced as well as metastatic.

You have approvals of HHIs and ICIs for the metastatic groups. I think these therapies go hand-in-hand. They would be used independently of one another, but as some trials have shown, the patients who are treated with checkpoint inhibitors had already been treated with HHIs and either didn't respond, had progression, and/or had intolerable AEs. For BCCs, I wouldn't say that ICIs are first-line therapy, although it can be considered first line in many cases. Either one can be used depending on the patient's risk factors. If you are going to use ICIs, you have to be able to manage the AEs effectively and early. But most patients do well and have manageable AEs.

A good safety profile is important. Cemiplimab is currently the only ICI approved for BCC. I think it [will be]

reserved for the more severe BCC, though. The definition of “not amenable to curative surgery” or “not amenable to curative radiation” means different things to different people. Maybe we use cemiplimab for patients with multiple tumors who have surgical fatigue. Maybe we won’t need to take their eye out to get the tumor out. Maybe they have had 15 or 20 surgeries and prefer to try something that is nonsurgical. There may be other things to think about.

**AJMC®: An evolving treatment spectrum for BCC includes these nonsurgical options. What are some of the managed care considerations you would have for the changing landscape?**

**SCHLESINGER:** From a managed care perspective, when you’re talking about treating larger tumors, a surgical approach also needs extensive care. You’re also looking at care with a lot of associated morbidities. If you’re doing a large surgery followed by multidisciplinary reconstruction—for example, you have a tumor in the mid-face or that can be recurrent, which is not uncommon—that tumor may involve several specialties. It may involve head and neck oncology or surgical oncology. It may involve more surgery—nose and throat—followed by radiation therapy. That care could run in the millions. In such cases, the ICI might be a more cost-effective option than the surgery and carry less morbidity for the patient especially as we learn and achieve better outcomes with ICIs over time.

Another case, from a managed care standpoint, is when there are multiple tumors. A patient may be coming in for multiple Mohs surgeries and reconstruction, and [those costs] can add up as well—not only for the health care system but also from [the standpoint of] a patient’s decreased productivity. Every Mohs surgery requires the patient to rest and be off work. That costs money to employers and to the patient. And so all of that recovery time can become an issue especially when there are multiple tumors or when there’s a very large tumor requiring a large reconstruction. It can be good to reach for a systemic therapy when there’s a large number of tumors that can be addressed with one therapy as opposed to repeated surgical intervention. I think from a managed care perspective, systemic therapy stands up there with the rest.

Certainly, Mohs surgery is the gold standard when it comes to tumors that are amenable to it that can have a reasonable chance of being completely removed with clear margins. That would be the original goal. It is very important if you can get clear margins because you have higher risk when you don’t get clear margins. Salvage radiation—where we’re going in to, say, radiate a tumor that we know is not clear—can have a poor outcome. Getting a clear margin is important if you’re going to be doing surgery. A systemic route may be another very viable option, even from a cost standpoint.

**AJMC®: We’ve seen more data for both HHIs and ICIs like cemiplimab. Are there new horizons for their potential usability or for systemic therapy in general? What more would you like to see?**

**SCHLESINGER:** There’s a lot to learn, and I think we’re just starting. These are very new therapies. The efficacy for ICIs with BCC being in the 20% to 30% range is good, but there’s a lot to be developed for the tumors that fail to respond. What do you do with patients who have intolerable AEs? Can we manage those? Are there other add-on medications? Are there new targets? Already, companies are looking into how to improve the efficacy and efficiency of our existing ICI therapies by adding on other medications to eradicate the tumor or reduce its size. I think we’ll also see other targets.

This is a rapidly moving time as you can see from the development of the COVID-19 vaccines. With current technology, we can go from target to commercial much more quickly. As we learn more about what receptors are available on tumors, we’ll be able to develop new targets or enhance the benefits. This is already happening. The research world is already looking into ways to make these drugs more effective: administering them in different ways, for instance. There’s a lot of advancement. We just want to see it continued to improve the efficacy of medications and safety. Our holy grail is 100% effective with no AEs. That is not achievable in some cases. However, the more we can get increased efficacy with decreased AEs, the more efficient we can consider our treatments from both health care cost and patient morbidity standpoints.

**AJMC®: Given the recent advances, what does the future of BCC treatment look like? What are your key takeaways when it comes to optimizing patient care?**

**SCHLESINGER:** The main thing to think about is the education of physicians and getting the word out about these treatments, which are still very new. Though there are many opportunities for patients to access them, these medications come through their physicians. The more we can get physicians educated about these new technologies and their availability in therapies, the better. Oftentimes a lot of these patients end up with these types of advanced tumors and are unfortunately underserved or subject to issues with health care disparity. It’s a population that oftentimes can benefit highly from these drugs: The patients who are coming in with the advanced tumors from the outset, in many cases, don’t have access to care and are coming in only when their tumors are already in an advanced stage. We can get even down to the primary care physicians to be aware that these technologies are there, so that these patients can be channeled into treatment. I think physician education is a key consideration. ♦







