ADVANCED BASAL CELL CARCINOMA:
HOW TO NAVIGATE CHALLENGING CLINICAL SCENARIOS WITH SYSTEMIC TREATMENT

OVERVIEW

Basal cell carcinoma (BCC) is a common type of skin cancer that can be challenging to treat in advanced stages. Join Drs. Karl Lewis and Aleksandar Sekulic as they discuss the importance of the hedgehog pathway in the pathogenesis of BCC and the role of hedgehog inhibitors in advanced BCC. Evidence related to the safety and efficacy of the approved hedgehog inhibitors sonidegib and vismodegib are discussed, with recommendations for optimizing their use. Case studies are utilized to share the faculty's experience in treating patients with hedgehog inhibitors, including strategies to manage resistance.

TARGET AUDIENCE

This activity is intended for a national audience of oncologists, dermatologists, dermato-oncologists, and Mohs surgeons.

LEARNING OBJECTIVES

- Explain how the target pathways of systemic treatment for advanced basal cell carcinoma (BCC) align with the current understanding of the pathogenesis of the disease
- Evaluate the profiles of and clinical data related to current and emerging systemic treatments to support the optimal care of patients with advanced BCC
- Create systemic treatment plans for patients with advanced BCC who are intolerant to hedgehog pathway inhibitors
- Identify opportunities to improve the management of patients with advanced BCC whose disease has progressed despite previous treatment with hedgehog pathway inhibitors

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Aleksandar Sekulic, MD, PhD

Hello and welcome to today's educational session named Advanced Basal Cell Carcinoma, How to Navigate Challenging Clinical Scenarios With Systemic Treatment. My name is Aleksandar Sekulic and I'm a dermatologist at Mayo Clinic, focusing primarily on skin cancers, including basal cell carcinoma. And I have with me, my colleague, Dr. Karl Lewis, and I'll let him introduce himself.

Karl D. Lewis, MD

I am Dr. Karl Lewis, from the University of Colorado. I'm a medical oncologist, specializing in the treatment of cutaneous malignancies.

INTRODUCTION

Malignant skin cancers fall into 2 broad categories, melanoma and nonmelanoma skin cancer. As a medical oncologist, the vast majority of what I see is melanoma, as that's a type of cutaneous malignancy that has a high propensity for metastasis. The nonmelanoma skin cancers are much more common and can lead to advanced and metastatic disease as well. These fall into multiple categories, basal cell carcinoma, squamous cell carcinoma, as well as other tumors, such as Merkel cell carcinoma, apocrine gland tumors, cutaneous T-cell malignancies, etc.

The epidemiology of basal cell carcinoma. Nonmelanoma skin cancer is the most common of all malignancies, but it accounts for less than 1% of cancer-related deaths. Greater than 1 out of 3 new cancers are skin cancers. So, this is a very prevalent tumor and the incidence increases with lighter skin complexion and increased ultraviolet light exposure.

It's estimated that there's about 5.4 million basal and squamous cell cancers diagnosed each year in the United States. 80% of these are basal cell cancers and that's over 4 million cases a year. The incidence in nonmelanoma skin cancers is estimated to have increased about 77% in the last decades, possibly due to continued lifestyle changes and sun exposure. And there is socioeconomic and psychologic burden of this disease.

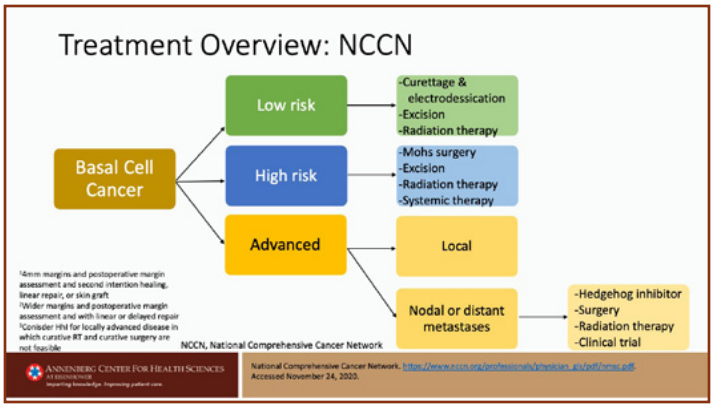
The development of basal cell carcinoma results from an interaction between numerous genes and environmental factors. And most of the mutations in basal cell carcinoma carry a UV-induced DNA damage signature. A key pathway in basal cell carcinoma is mutations in the hedgehog pathway. The hedgehog pathway is a series of proteins. It's a highly conserved signaling pathway that plays a crucial role in embryogenesis, and of the multiple alterations in basal cell carcinoma, hedgehog pathway alterations are nearly ubiquitous.

Hedgehog pathway is a series of proteins, mutations can occur in the patched 1 (PTCH1) gene, as well as the smoothened gene, but other proteins in the hedgehog pathway, such as suppressor of the fused gene (Sufu), can also be altered.

BEGIN SYSTEMIC TREATMENT: HEDGEHOG PATHWAY

Aleksandar Sekulic, MD, PhD

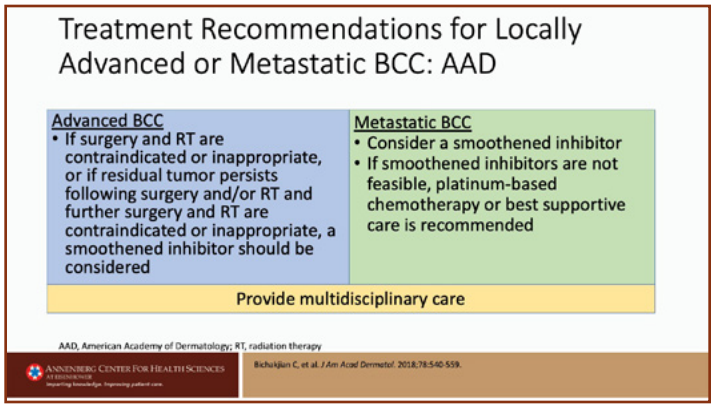
When we think about the treatment of basal cell carcinoma, there are multiple guidelines, one of the most prominent being the National Comprehensive Cancer Network (NCCN) guidelines. And the slide in front of us illustrates the general recommendations for treatment of basal cell carcinoma. If we divide basal cell carcinoma into those with the low risk, those are typical early tumors that are easily treated with simple



surgical methods. The high-risk local tumors will require a little bit more involved treatments, such as Mohs surgery to ensure that the tumor is microscopically fully removed. Sometimes, this will require radiation therapy or even systemic therapy in some cases.

But the truly complicated cases are more of the advanced group of basal cell carcinoma cases, which really include locally advanced disease and nodal or distant metastatic disease. These are the types and groups of patients that historically had represented a group with an unmet medical need.

When we think about advanced basal cell carcinoma in terms of locally advanced basal cell, the surgery and radiation therapy sometimes are not appropriate or are not expected to achieve clearance.



Those are the cases where additional therapeutic options were necessary. Metastatic basal cell carcinoma historically has been a neglected area, and only few small study cohorts or case studies have been reported without really systematic evaluation of treatment options for these patients.

The key point in managing patients with either locally advanced or metastatic basal cell carcinoma is that often it requires multidisciplinary care and coordination of that care.

As actually Dr. Lewis mentioned earlier, hedgehog signaling pathway is the principal driver of basal cell carcinoma in almost all cases of disease. Therefore, development of targeted inhibitors of the hedgehog signaling pathway became a high priority, yielding 2 inhibitors that are now FDA approved. Sonidegib is a small molecule smoothened inhibitor that was approved for treatment of locally advanced basal cell carcinoma.

Vismodegib, also a targeted smoothened inhibitor, is approved for both locally advanced basal cell carcinoma, as well as metastatic basal cell carcinoma. In both cases, the population that is targeted really is the population that is not considered as candidates for surgery or radiation therapy.

Two Hedgehog Inhibitors Currently Approved for Locally Advanced BCC by FDA

Hedgehog Inhibitor	Indication	Dosage & Administration
Sonidegib (Odomzo)[1]	Adult with laBCC that has recurred following surgery or RT, or those who are not candidates for surgery or RT	200 mg PO QD on an empty stomach
Vismodegib (Erivedge)[2]	Adults with laBCC that has recurred following surgery or those who are not candidates for surgery and who are not candidates for RT	150 mg PO QD

BCC, basal cell carcinoma; laBCC, locally advanced basal cell carcinoma; RT, radiation therapy

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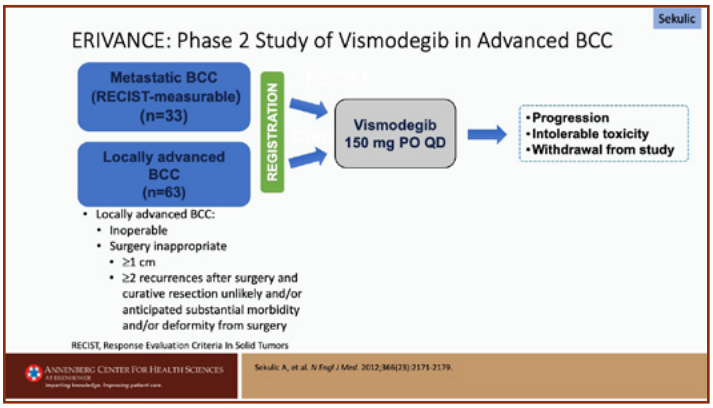
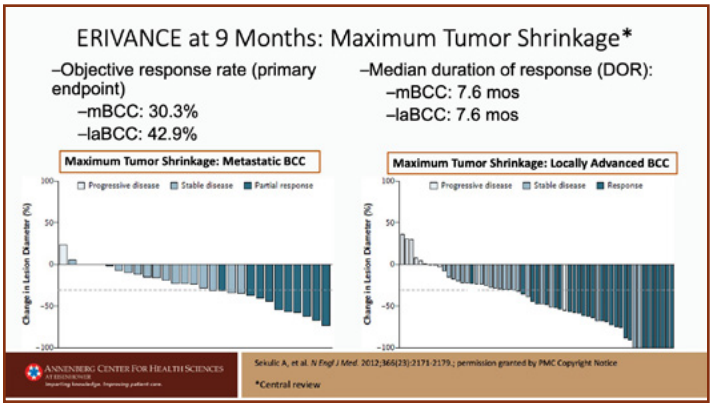
1. Odomzo [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; July 2020.
2. Erivedge [package insert]. South San Francisco, CA: Genentech USA, Inc.; August 2020.

BEGIN SYSTEMIC TREATMENT: VISMODEGIB

Aleksandar Sekulic, MD, PhD

The ERIVANCE trial was a phase 2 clinical study of vismodegib in advanced basal cell carcinoma in patients with both metastatic and locally advanced basal cell carcinoma. These patients were treated with 150 mg of vismodegib until they either progressed, encountered intolerable toxicities, or withdrew from the study for other reasons.





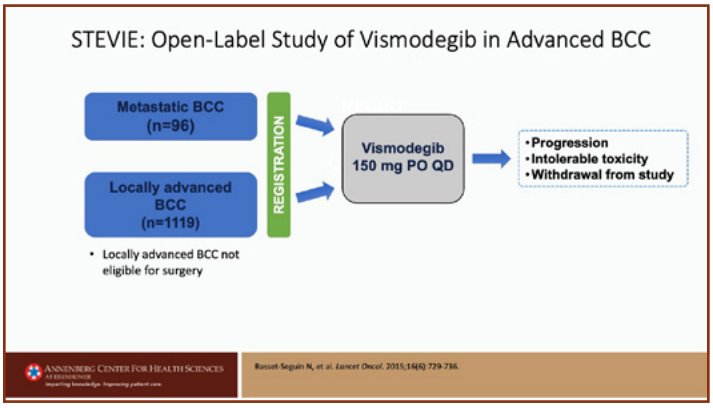
The data from this study very clearly showed that there are significant responses in the vast majority of patients treated. When the responses were assessed by an independent group, there were measured at 30% in a metastatic cohort and 42.9% in locally advanced basal cell carcinoma cohort.

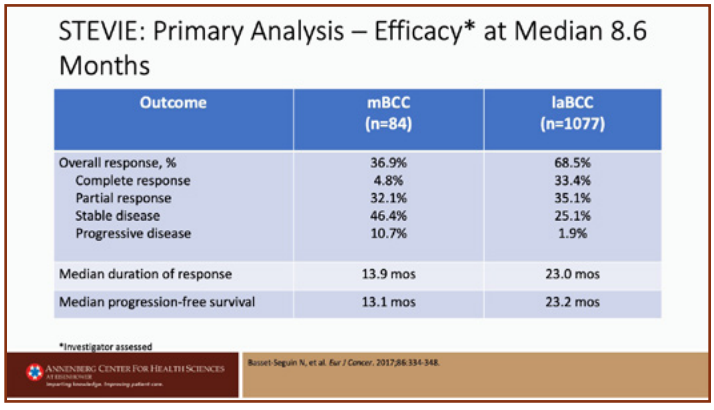
These types of responses are clearly illustrated by photographs of patients that have been treated as the one in front of you.

Importantly, when we look at the longer-term efficacy of vismodegib, and this is measured at 39 months for vismodegib this time by investigators, not by an independent panel, the objective response rate was assessed as at 48.5% for metastatic BCC and 60.3% for locally advanced BCC.

One issue that has become very well understood and significant in the treatment of patients with hedgehog pathway inhibitors are adverse events. And these really are not random toxicities. These are on-target effects on tissues that still require a hedgehog pathway in an adult organism. The most common effects that patients find most bothersome usually are muscle spasms, changes in taste, either alterations of taste or lack of taste, loss of hair, sometimes weight loss, fatigue, and so on.

Similar to the ERIVANCE study, the STEVIE study has enrolled metastatic and locally advanced basal cell carcinoma patients, which were then treated with vismodegib. In this study, 499 patients were enrolled and the efficacy, which was, in this case, measured only by the investigators was similar to what was seen with the ERIVANCE study.





At median 8.6 months, the overall response rate was deemed at 36.9% for the metastatic cohort and 68.5% for locally advanced basal cell carcinoma cohort.

STEVIE: Primary Analysis – Safety at Median 8.6 Months

Most common TEAE	
Any AE	98%
Muscle spasm	66%
Alopecia	62%
Dysgeusia	55%
Weight decreased	41%
Decreased appetite	25%
Asthenia	24%

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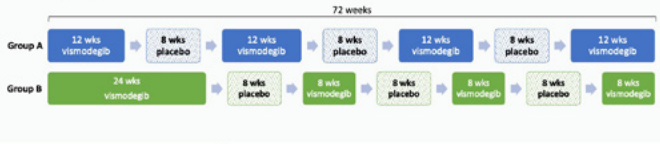
Basset-Seguin N, et al. *Eur J Cancer*. 2017;86:334-348.

MIKIE: Intermittent Dosing Regimens With Vismodegib

- Goal: Assess safety and efficacy of long-term intermittent dosing of vismodegib in patients with multiple basal cell carcinomas
  - ≥1 histologically confirmed and ≥6 clinically evident
- All patients received vismodegib 150 mg/d
- Primary endpoint: % reduction in number of clinically-evident BCCs at wk 73



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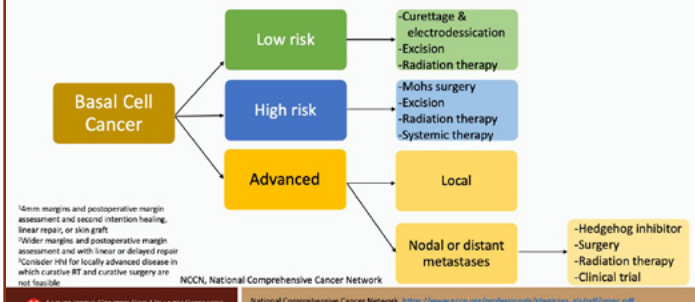
Dreno B, et al. *Lancet Oncol*. 2017;18(3):404-412.

As was seen in ERIVANCE, the adverse event profile was very, very similar.

The third study that's worth mentioning in development of vismodegib was a study called MIKIE, which was looking at the question of intermittent dosing regimens with vismodegib. And this study was pursued specifically because of the toxicities and issues with tolerating the longer term treatment with this type of medication. This study has looked at 2 different dosing regimens, one altering 12 and 8 weeks of on and off, respectively. And a second group that was looking at 24 weeks initial treatment, and then 8 weeks off and on to see what may be the better way, and better tolerated way, whether the efficacy is maintained.

And it appears that the efficacy was very, very comparable between 2 groups. And when compared with previous experience that was seen in studies, such as ERIVANCE and STEVIE, the efficacy was very comparable. So were the side effects, and there were no surprises there.

Treatment Overview: NCCN



[1]4mm margins and postoperative margin assessment and second intention healing, linear repair, or skin graft
[2]Wider margins and postoperative margin assessment and with linear or delayed repair
[3]Consider HH for locally advanced disease in which curative RT and curative surgery are not feasible

NCCN, National Comprehensive Cancer Network

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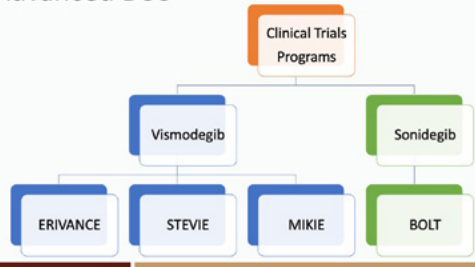
National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf. Accessed November 24, 2020.

BEGIN SYSTEMIC TREATMENT: SONIDEGIB

Aleksandar Sekulic, MD, PhD

As I mentioned, the second drug that was developed in this space was sonidegib, which is also a smoothened inhibitor, as is vismodegib. And the most significant study to mention is the BOLT study, which is a phase 2 study of sonidegib in advanced basal cell carcinoma. This study which was very similar to previously mentioned studies, such as ERIVANCE, has enrolled patients with either metastatic or locally advanced BCC. The difference here was that 2 different doses were assessed, 1 at 200 mg daily, and one at 800 mg daily.

Clinical Trials Programs of Hedgehog Inhibitors for Advanced BCC



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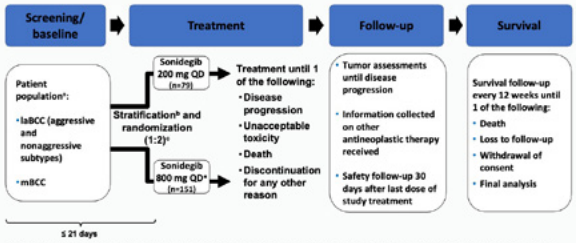
BOLT: Phase 2 Study of Sonidegib in Advanced BCC



[a]Patients previously treated with sonidegib or other Hh pathway inhibitors were excluded. [b]Patients were stratified based on stage, disease histology for laBCC (nonaggressive vs aggressive), and geographic region. [c]Patients were randomized to receive sonidegib 200 mg QD (lowest dose level tested that showed antitumor activity) and 800 mg QD (highest well-tolerated, biologically active dose) based on the phase 1 study.[4]
*Dosing regimen not approved by US FDA

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Migden M, et al. *Lancet Oncol*. 2015;16(6):716-728.

The response with sonidegib was seen in both the 200 and 800 mg doses. But the 200 mg dose has shown better tolerability while having similar efficacy. The response rate, objective response rates for patients that were treated with the 200 mg dose per day was 56% in locally advanced basal cell carcinoma and 8% in metastatic basal cell carcinoma.

Given the low number of patients accrued into the metastatic basal cell carcinoma cohort, sonidegib was pursued with the FDA for approval for locally advanced, but not metastatic, disease. The safety of the drug was very similar to what we've seen with vismodegib.

BOLT: Efficacy* at 42 Months

% of Patients who remained on treatment at 42 mos: 200 mg (8%); 800 mg (3.3%)

Outcome	laBCC		mBCC	
	200 mg (n=66)	800 mg (n=128)	200 mg (n=13)	800 mg (n=23)
Objective response	56%	46%	8%	17%
Complete response	5%	2%	0%	0%
Duration of response, median	26.1 mos	23.3 mos	24.0 mos	NE
Progression-free survival, median	22.1 mos	24.9 mos	13.1 mos	11.1 mos
Time to tumor response, median	4.0 mos	3.8 mos	9.2 mos	1.0 mo

NE, not estimable *Central review

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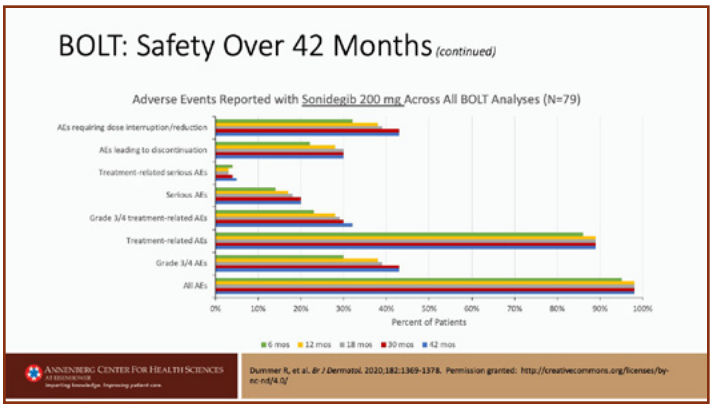
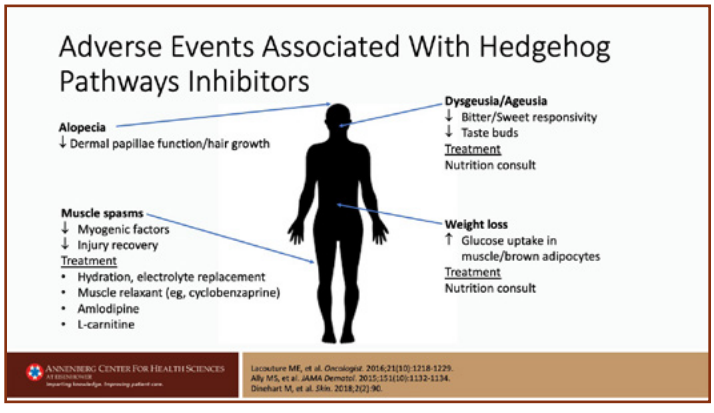
Dummer R, et al. *Br J Dermatol*. 2020;182:1369-1378.



OPTIMIZING HEDGEHOG INHIBITORS

Karl D. Lewis, MD

As has been mentioned, one of the big issues with hedgehog pathway inhibitors—smoothened inhibitors—is they have a very specific toxicity profile. And these are class-dependent. Alopecia is a problem. Dysgeusia or ageusia, the loss of taste, is a major issue for these patients. Consequently, patients can lose weight, and muscle cramping is a big issue. These tend to occur with both agents, as I said, it's a class effect. And trying to just mitigate their severity is important in trying to maintain drug adherence.



Nutrition consults and getting patients to maintain their weight can be very important. In terms of controlling muscle spasms, hydration and electrolyte replacement is likely important, although there is limited data on pharmacological interventions, such as calcium channel blockers or L-carnitine, but they may play a role in ameliorating some of the toxicities.

In terms of the hedgehog inhibitors, the pros of the drug are they are oral, and they have high efficacy, and they can achieve histological clearance of tumor. But the cons are they're not very well tolerated, and primary and secondary resistance can develop.

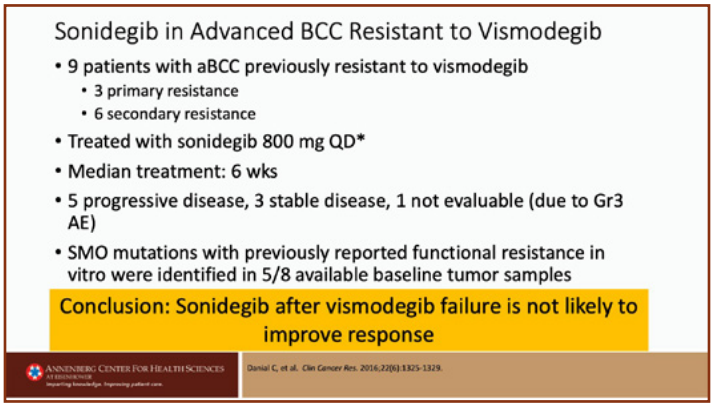
Monitoring patients during hedgehog inhibitor therapy. There's no clear guidelines, but it's generally as you would monitor somebody on any anticancer therapy, you certainly need to assess tumor burden at baseline and how the tumor is responding to the therapy. And that's both with imaging measurements, physical exam measurements, photography, as sometimes—oftentimes—these tumors are superficial and visible.

Patients should be seen monthly to every 3 months. Total skin exam should be performed. There is some data out there that shows patients on hedgehog inhibitors may be more susceptible to developing other nonmelanoma skin cancers, specifically squamous cell carcinoma. Need to follow up for their adverse event management, making sure their weight is maintained. I do tend to check laboratory studies on these patients every 1-3 months, although CBC abnormalities tend to be uncommon, but we need to follow electrolytes. They can cause creatine kinase (CK) elevations, those should be followed.

And one important thing is to emphasize effective contraception. These drugs are teratogenic and we certainly do not want patients to become pregnant while they are on these agents. The hedgehog pathway, as stated earlier, is very important in embryogenesis. So effective contraception is crucial.

Strategies to improve patient inherence. I think it's important that patients know exactly what to expect when they are on these treatments. The side effects are a class effect. So, almost every patient develops an adverse event related to hedgehog inhibitor therapy. There are varying degrees, but patients need to know that in all likelihood they will lose their hair. They will have some diminishing of their taste, if not complete loss of taste, and be aware of muscle cramping.

Women, particularly for hair loss, can wear a wig. Make sure that patients hydrate, stretch, do certain things to ameliorate some of the muscle cramping, that can increase adherence to the medication.



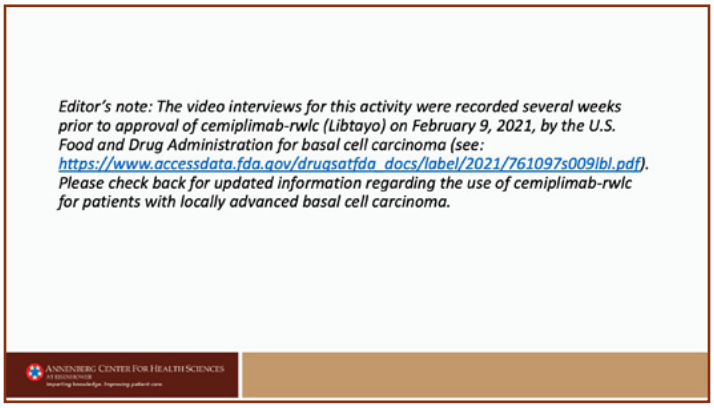
Mechanisms of resistance. That is a problem, of course, with any targeted therapy, and it's no exception with the smoothened inhibitors. There has been some look at this. There was a study that looked at 16 patients who developed resistance to hedgehog inhibitor therapy. And the majority of resistance mechanisms were alternative mutations in smoothened.

This study, published, looked at 9 patients with advanced basal cell carcinoma that became resistant to vismodegib, and they were treated with sonidegib. Three of those patients had primary resistance, 6 secondary resistance, and the median treatment on sonidegib was 6 weeks. Five of those patients developed aggressive disease. There were 3 cases of stable disease. One patient was not evaluable as they had a toxicity.

But 5 of the 8 samples that were available for tumor analysis demonstrated that smoothened mutations with the previously reported functional resistance in vitro were identified in these patients. So, the overall conclusion is that the alternative hedgehog is unlikely to improve responses in patients who have developed resistance to 1 of the agents.

EMERGING AGENTS

Karl D. Lewis, MD

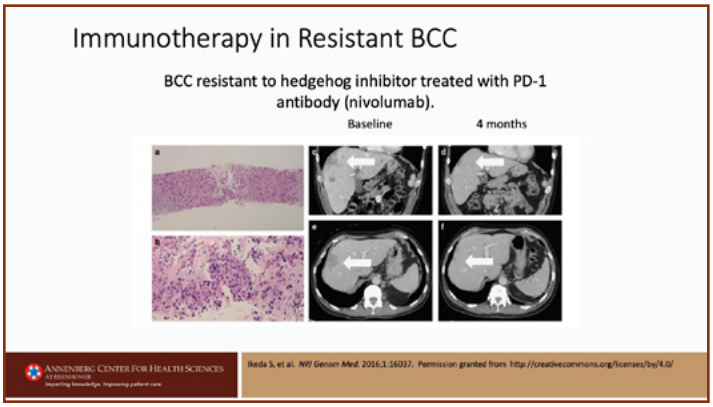


What are some of the emerging agents for advanced basal cell carcinoma? Well, one thing to think of is immune therapy. And should this be used in patients who have resistant basal cell carcinoma to smoothened inhibition? The rationale for this would be that the immune system plays a critical role in surveillance and eradication of nonmelanoma skin cancers.

And this is demonstrated, for example, in solid organ transplant patients. There's an increase of 65-fold for cutaneous squamous cell carcinomas in these patients, and that's, of course, well-known, but there's also a 10-fold increase in basal cell carcinoma in transplant patients on immunosuppression. The tumor microenvironment of UV-induced tumors can be immunosuppressive and the innate immune system can eradicate UV-associated tumors. And this is demonstrated by the use of imiquimod, which is a Toll-like receptor agonist, in basal cell carcinoma.

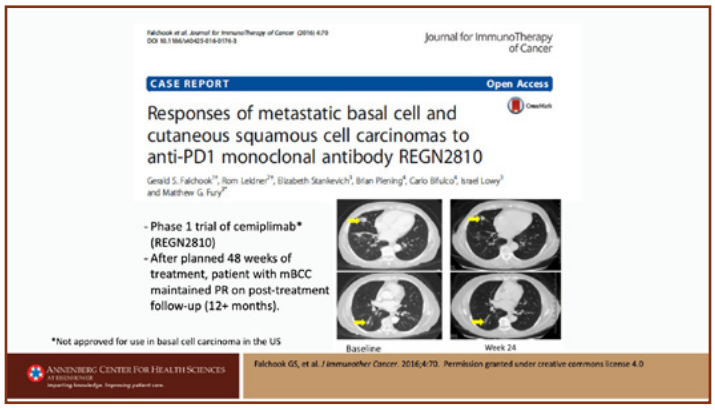
And certainly there's activity of immunotherapy on other cutaneous malignancies. Does this relate to the high mutation burden that these cancers have that's possibly a biomarker for effectiveness of immunotherapy? We know there are lots of data of treating melanoma with immunotherapy, Merkel cell carcinoma treated with PD-1 and PD-L1 antibodies. There is now a PD-1 antibody approved to treat advanced cutaneous squamous cell carcinomas.

And so why not? It seems to work in other cancer types, so I think it's worth investigation in advanced basal cell carcinoma.



There are previously a number of case reports of basal cell carcinomas that were resistant to hedgehog therapy, responding to immunotherapy. There was a case of basal cell carcinoma resistant to hedgehog inhibitor treated with the anti-PD-1 nivolumab and baseline tumor measurements in this patient, with liver metastasis that are markedly improved at the 4-month time point.

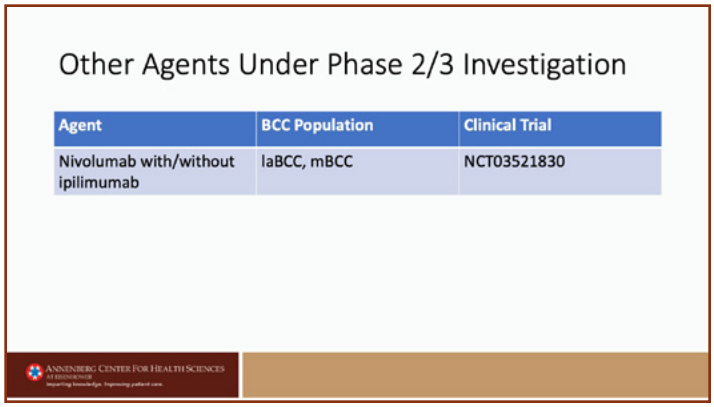
In the early phase study of cemiplimab in patients with multiple tumor types, they did include patients with cutaneous malignancies, including a patient with basal cell carcinoma. And at a planned 48 weeks of treatment, a patient with metastatic basal cell carcinoma on this study maintained a partial response on post-treatment follow-up, at least, for at least 12 months after therapy. So, there is some early case report evidence of activity of immunotherapy in this disease.



Recently reported at the 2020 European Society of Medical Oncology (ESMO) meeting was a phase 2 study of cemiplimab for locally advanced basal cell carcinoma. This is a study that included 2 cohorts of patients, metastatic basal cell and locally advanced basal cell. As reported at ESMO 2020, the locally advanced basal cell carcinoma data was available. It was an open-label study of using cemiplimab every 3 weeks for up to 93 weeks or until disease progression, and median follow-up was 15 months.

The median baseline tumor mutation burden tended to be higher in patients who were responding than those who did not respond, but among the 84 patients that were treated, with locally advanced basal cell carcinoma, there was an overall response rate of 31%. Five of those patients attained complete response. 21% of those patients had a partial response and importantly, 85% of the responses are ongoing at 12 months. And the median duration of response had not been reached.

The adverse events in this study were consistent with adverse events with PD-1 antibodies in general, near autoimmune in nature and, most fortunately, were relatively mild. 17% of the patients did discontinue treatment due to adverse events.



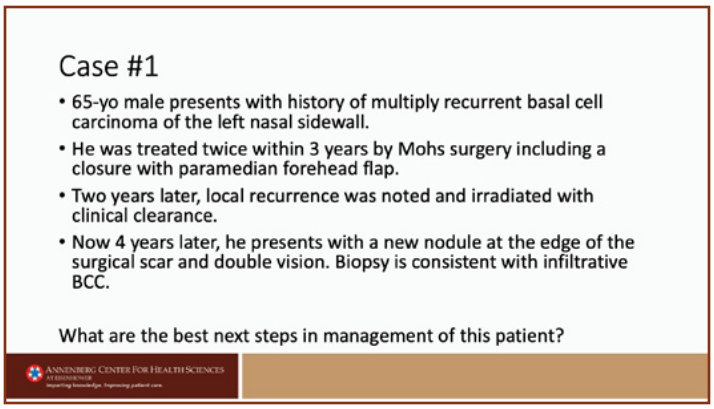
There are other studies looking at immunotherapy in advanced basal cell carcinoma, including this study with nivolumab with or without ipilimumab, in locally advanced or metastatic disease.

CASE STUDIES

CASE #1

Aleksandar Sekulic, MD, PhD

The first case is a case of a patient, a 65-year-old male who presented with history of multiple recurrent basal cell carcinoma of the left nasal sidewall, which was treated twice within 3 years by Mohs surgery and requiring closure with paramedian forehead flap after the second surgery.



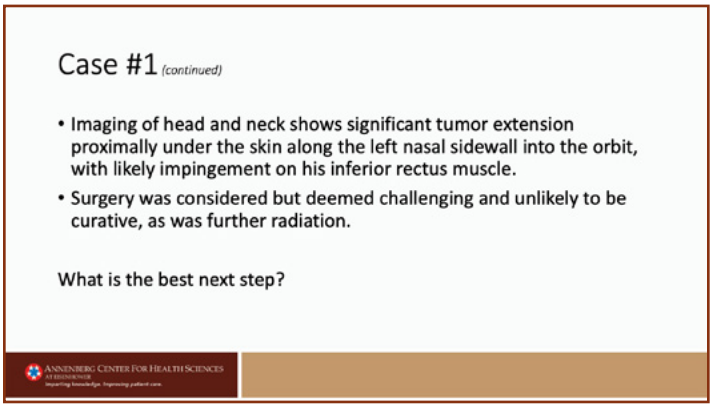
Unfortunately, 2 years later, he developed a recurrence which was then treated by radiation. Now 4 years after the radiation, he presents with a new nodule at the edge of the surgical scar, and also complains of double vision. The biopsy of the visible recurrent lesion is consistent with an infiltrative basal cell carcinoma. Dr. Lewis, what would you do at this point?

Karl D. Lewis, MD

Given the recurrence and the symptoms that he's experiencing, specifically the double vision, I think that's very concerning for a deeply infiltrated tumor into underlying structures. And so I think he needs imaging to get a sense of the extent of disease.

Aleksandar Sekulic, MD, PhD

Indeed, he was imaged and staged, and the imaging showed that in addition to the visible tumor, there was extension of the tumor along the nasal sidewall into the inferior part of the orbit with impingement on the inferior rectus muscle, explaining his double vision. So, given the prior



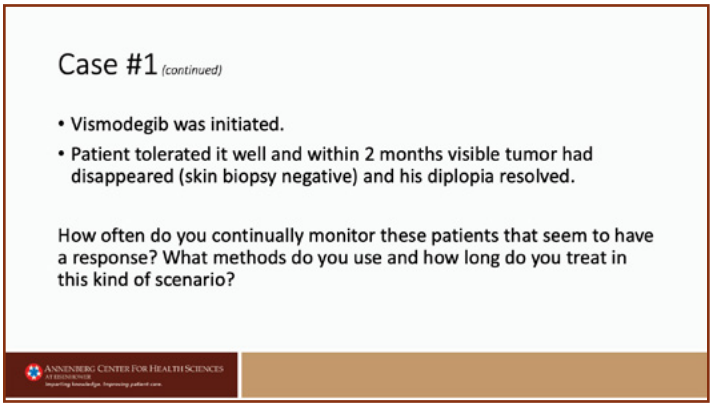
surgery and multiple surgeries and radiation, surgery was not deemed an appropriate option, nor was radiation. What would you be thinking as next steps for this patient at this point?

Karl D. Lewis, MD

This is a patient that really falls into that category of locally advanced basal cell carcinoma. And so this is a patient who I think the best chance of getting some meaningful benefit would be with systemic therapy. And so I think he's a good candidate for initiation of hedgehog inhibitor treatment.

Aleksandar Sekulic, MD, PhD

Indeed, he was started on vismodegib and tolerated it well, and actually had a fairly rapid response. And within 2 months, the visible tumor has disappeared, and his double vision also resolved. Now, the question in this kind of scenario often is how do you continually monitor these patients that seem to have a response? What methods do you use and how long do you treat in this kind of scenario? What would be your take on this?



Karl D. Lewis, MD

Well, continued physical exam, looking for any obvious progression visibly. Also, since he has imaging findings, it's important to continue to image him, looking at the deeper tissues. But the fact that his symptoms have resolved and as long as he maintains and stays symptom free, that's very important. The big question is how long do you treat patients like this? And that's really unknown.

This is a drug, as we talked about, that's difficult to maintain on for long-term. So, do you stop at its best response, do you keep going? It's really unknown. In practice, I would tend to continue to treat him, and the longer he can stay on drug, the more hope I would have that he could potentially clear his tumor as there are a number of complete responses on the clinical trials with vismodegib. So I would continue him on therapy for the time being, watching very carefully for adverse events.

Aleksandar Sekulic, MD, PhD

And indeed, that is what was done. And the patient was monitored both by physical exams and by imaging, and maintained on therapy for a period of approximately 8 months. And then the therapy was stopped and the patient continued to be closely monitored.

I think previous data that we described with vismodegib showed clearly that the efficacy did not significantly suffer in patients that have had treatment breaks. And since then, multiple investigators have reported efficacy of these drugs, even after drugs are stopped for a period of time and then reinitiated. I think also this case was educational in terms of not

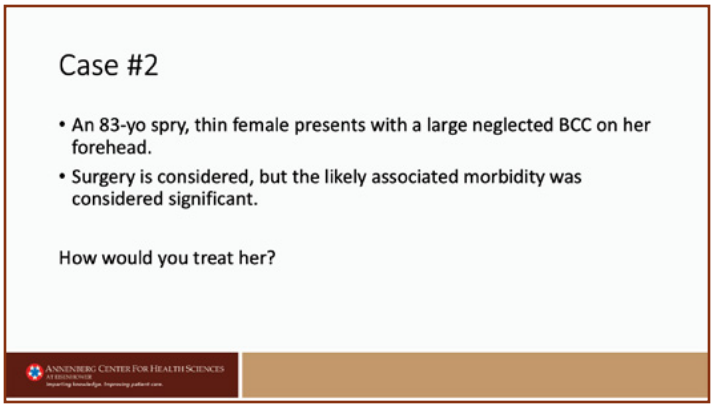
only describing the appropriate patient for treatment with these types of medications, but also describing the challenges in, and importance of, both the physical examination and deeper imaging in patients where there is a deeper component.

CASE #2

This is an 83-year-old, spry, thin, female who presents with a large neglected BCC on her forehead. Surgery was considered, but the likely associated morbidity was considered significant, and another option was sought. What would you be thinking for this patient?

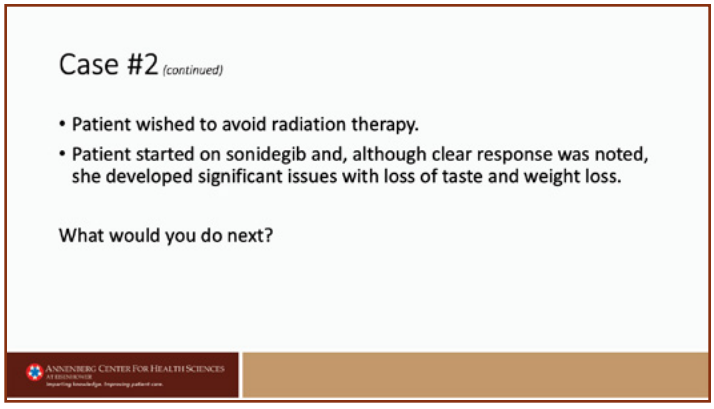
Karl D. Lewis, MD

Without seeing the tumor, one thing that could be considered is radiation therapy. These tumors tend to be radiosensitive. So, radiation evaluation would be worthwhile. The other alternative is systemic therapy; you know, neglected basal cell carcinomas, not easily amenable to resection. These can fall into the category of locally advanced disease and would be appropriate for hedgehog inhibitor therapy.



Aleksandar Sekulic, MD, PhD

I would agree, radiation in somebody who is 83 years old is definitely a reasonable option. This patient was not keen on radiation and she opted for systemic therapy. So, she was started on sonidegib, and demonstrated a response within 3 months, but has had significant issue with side effects. Primarily, she complained of lack of taste and weight loss. And as I mentioned, she was a fairly thin, elderly female, although in a very good shape. What would you do at this point?

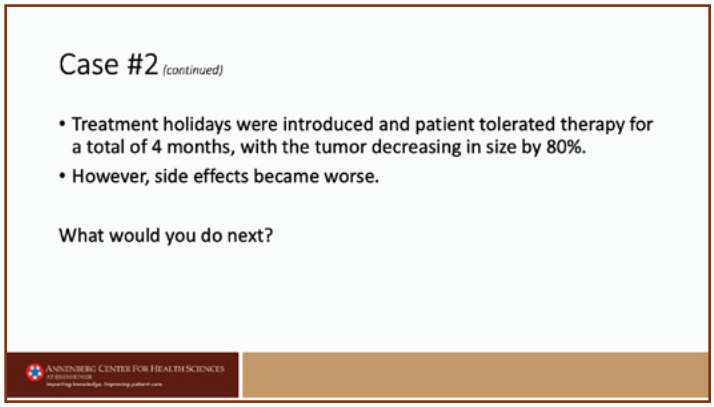


Karl D. Lewis, MD

Toxicities are a big issue with hedgehog therapies. The way that I generally try to manage these, if patients seem to be benefiting in terms of tumor response, is I really am fairly lenient with drug holidays. So, I tend to kind of treat to toxicity, give them an extended break, let the side effects diminish significantly, and try to get them back on drug. The MIKEY study, as presented earlier, had those specific breaks built in. I haven't taken a specific time to practice. I tend to just see how patients are doing clinically and manage the breaks accordingly.

Aleksandar Sekulic, MD, PhD

Yes, and in this patient, definitely that was an option. And she was very pleased with her response, but also very bothered by the side effects. So, she opted for intermittent treatment, which was pursued. And after about 4-5 months, the tumor has shrunk down by at least 80%. Unfortunately, her side effects with treatment have worsened to the point that even short courses of treatment became intolerable for her. What would you think of at this point?



Karl D. Lewis, MD

Since she had such a good tumor response, it's not unreasonable to reintroduce the option of local therapy. There are some limited data out there in terms of using this neoadjuvantly, trying to shrink the tumor, make it amenable to resection, and proceeding with local intervention. So, depending on what this looks like, and if surgery is deemed more reasonable now, that would be an option. Also, reintroducing the option of radiation now that the tumor is smaller. So, given the fact that she's had what looks like a very good partial response with significant issues of toxicity, it might be reasonable to look at local therapy at this point.

Aleksandar Sekulic, MD, PhD

Yes, and both of those options were discussed with the patient, with radiation being a fairly good option for her at this point. But she was still resistant to radiation. She just did not like that idea. And she opted actually for surgery, and the tumor has shrunk significantly. The surgery was done with more ease than was initially the case. And she did well. She passed away 6 years later from unrelated causes.

I think this highlights the important point that you mentioned that an inoperable tumor may be turned potentially into operable—sort of a neoadjuvant-type of approach. Also, what is important here, I think, is that when we approach people that are elderly, and especially those that are

thin, the side effects of these drugs, and particularly lack of taste, loss of taste, alterations of tastes, and weight loss, may become significant if you're talking about somebody who already is compromised in this space.

So, ensuring that adequate, not only hydration, but adequate nutrition, is provided, is important.

Karl D. Lewis, MD

And, and that's where treatment breaks can be important as well. What hasn't been mentioned is that these drugs cannot be dose reduced, the dose is the dose. And so, those reductions are not really an option. I always get nervous about alternative dosing schedules every other day, 3 times a week, whatever it may be, because I think that there's data, particularly with vismodegib in terms of drug levels, that daily dosing may be very important. So, my general management of these side effects as stated earlier, is the drug holidays.

CASE #3

This is a case of a 56-year-old male who has a history of basal cell carcinoma on the left shoulder, that was treated with excision. About a year after the initial excision, he developed enlarged lymph nodes in the left neck that were biopsy-proven to be regionally metastatic basal cell carcinoma. He underwent a lymph node dissection followed by post-operative radiation therapy. And on the surgery, 6 of 24 lymph nodes were involved with basal cell carcinoma.

He was watched at that point, and a few years later he was found to have enlargening pulmonary lesions that were biopsied and consistent with metastatic basal cell carcinoma. So, he was treated with vismodegib. He had poor tolerability, some response to the therapy, but was on and off treatment for a year-and-a-half. And eventually a CT scan showed progressive disease in the lungs. So, I would turn it to you and say, you know, what are his options at this point?

Aleksandar Sekulic, MD, PhD

Yes, I think this is one of those challenging scenarios that clearly illustrates the need for other options. And, historically, in these patients, we have considered other options, particularly platinum-based agents, which have been described in small cohorts of patients historically as being active and potentially useful. But that data is not significant and not structured enough and robust to really support the use of these agents widely.

With the onset of immunotherapy, and as we reviewed earlier, numerous cases that were described as very effective in basal cell carcinoma, as well as the ongoing clinical trials, particularly the clinical trial of cemiplimab in basal cell carcinoma, I would be thinking about immunotherapy.

Now, of course one needs to look at the patient in their entirety and assess whether immunotherapy is an appropriate therapy, as we do with other cancers. Is it a transplant patient? Is the patient on immunosuppression? Do they have potentially significant autoimmune disease? All of those issues that we would look at and balance with potential benefits of the therapy.

Karl D. Lewis, MD

Yes, I completely agree. Systemic therapy obviously is what's needed here. He has metastatic disease. He had some response to the hedgehog inhibitor therapy. Responses tend to be lower as demonstrated in the clinical studies for metastatic, as opposed to locally advanced disease. And this is a space that really is an unmet need. So, platinum-based chemotherapy was considered. This otherwise healthy gentleman could certainly tolerate chemotherapy, but as mentioned, the studies on that and questions of durability.

He did not have any significant comorbidities, was not immune suppressed, did not have any autoimmune toxicities. And he was thought to be a good candidate for immunotherapy. And we were able to obtain immunotherapy—a PD-1 antibody—for him, and he received that for about a year of treatment and had an excellent partial response to therapy. Still had 1 long lesion that remained, but it had decreased from baseline. He stopped therapy and he's been off treatment now, pushing 3 years, maintaining that good, partial response to the PD-1 antibody.

Aleksandar Sekulic, MD, PhD

I think this case nicely summarizes not only the importance of looking at the spectrum of options, but also the new emerging options that potentially are going to be available for our patients in the near future. And immunotherapy has had a significant impact already on multiple other cancers, including particularly, skin cancers.

SUMMARY

In summary of today's educational activity, we have defined what advanced basal cell carcinoma is, including both locally advanced and metastatic disease, as entities that historically represented an area of unmet medical need. This was addressed initially by development of hedgehog pathway inhibitors, which address the pathway that is a driver of this disease.

Two inhibitors that were approved in this space, including sonidegib and vismodegib, are both highly active, both with very good activity in locally advanced basal cell carcinoma and approved for locally advanced basal cell carcinoma. However, the class effects of these drugs on adult tissue that still rely on natural pathway are significant. And as such, often can be treatment-limiting.

In patients where that is the case, or in patients where the response is not achieved, or patients that recur and relapse after treatment with these drugs, new options are needed. And those emerging opportunities, particularly, include an exciting opportunity of immunotherapies, which are showing, in preliminary data, significant efficacy.

Beyond that, of course, we all are starting to think about further options, such as combination of therapies, including both immunotherapy and, potentially, targeted therapies. But definitely the landscape and the opportunities of therapies for patients with these types of diseases have dramatically changed over the last decade. And we look forward to new options and better options for our patients.

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