Slide 1 – Title Slide

Emily Stamell Ruiz, MD: Welcome to the CME certified activity titled, “Cutaneous Squamous-Cell Carcinoma, Managing Advanced Disease in the Era of Immunotherapy.” This educational activity is jointly provided by USF Health and Rockpointe and supported by an independent educational grant from Regeneron.

Slide 2 – Faculty

My name is Emily Stamell Ruiz. I’m the director of Dana-Farber and Brigham and Women’s High-Risk Skin Cancer Clinic, and I’m also joined by my colleague, Anne Silk who is medical oncologist at Dana-Farber Cancer institute.

Slide 3 - Disclosures

The faculty and non-faculty disclosures are listed here. We will take a few minutes to give you the opportunity to review these.

Slide 4 – Educational Objectives

The following are the educational objectives. At the conclusion of this activity, participants should demonstrate the ability to outline the diagnostic evaluation of patients with cutaneous squamous-cell carcinoma, describe commonly used systems for staging cutaneous squamous-cell carcinomas, review the current understanding of the path of physiology of advanced and metastatic disease, review current recommendations for developing individualized management plans for advanced and metastatic tumors, including the need for a multidisciplinary team and describe the
efficacy and safety of immune-targeted agents, newly approved for the management of cutaneous squamous-cell carcinoma.

**Slide 5 - cSCC: Incidence in the United States**

I’d like to begin the talk by reviewing the epidemiology and incidents of cutaneous squamous-cell carcinoma in the United States. Cutaneous squamous-cell carcinoma is the second most common cancer in our country. It’s second after basal cell carcinoma. In fact, newer incidents estimates are found at the number of cutaneous squamous-cell carcinomas diagnosed each year is almost the same as that of basal cells. This is primarily due to arising incidents with an increase of over 250% from the 1980s to the 2000s. Squamous-cell carcinoma is not captured in National Cancer registries. However, it is estimated that approximately one million tumors are treated each year. While most tumors have an excellent prognosis and are cured with surgery alone, a small subset will develop a poor outcome. Approximately 5% of tumors will develop a local recurrence, 4% will develop a nodal metastasis and 2% of patients will die from their disease.

**Slide 6 – Risk Factors for and Staging of cSCC**

Since cutaneous squamous-cell carcinomas are so common, it is important to risk-stratify tumors, so that we can identify those at risk for poor outcomes. There are certain risk factors that increase poor outcomes. Some are used as part of the current primary tumor staging systems.

**Slide 7 – Risk Factors for Local Recurrence and Metastases**

Important tumor risk factors can be divided into anatomic and histologic features. In the coming slides, I will review the different risk factors listed on this slide.
Slide 8 – Anatomic Risk Factors

Tumor diameter has been shown to increase both recurrence, metastasis and death from disease. Tumors above 2 cm have a three times of recurrence, six times risk of metastasis, and 19 times increase in disease-specific death. The NCCN guidelines categorize a number of locations as high risk, although it is important to note that the current primary tumor staging systems do not consider location as a risk factor. Studies have shown, however, that tumors on the ear and lip have a 1.3 times risk of local recurrence, 2.3 times risk of metastases, and over 4.5 times risk of disease-related death.

Slide 9 – Risk Factor: Perineural Invasion

The next important risk factor is perineural invasion, specifically of large-caliber nerves, which is defined as invasion of nerves at the diameter or 0.1 millimeters or greater. This has been shown to increase local recurrence metastasis and disease-specific death. On the other hand, small-caliber nerve invasion has not been associated with poor outcomes. However, one study did show an increased risk of poor outcomes with tumors that had multifocal perineural invasion, which was defined as PNI of two or more nerves. The current staging systems only include large-caliber PNI as a risk factor. Since most surgeons and pathologists have a micrometer to measure nerve caliber, nerves in the subcutaneous fat, or deeper, are considered large-caliber as these typically measure 0.1 millimeters or larger.

Slide 10 – Risk Factor: Tumor Differentiation

Tumor differentiation is graded as well, moderate, or poor. Poor differentiation is associated with the increased risk of local recurrence and metastasis and disease-
specific death. Since grading differentiation is not standardized and varies based on a pathologist evaluating the histology, not all current staging systems include differentiation as a risk factor.

Slide 11 – Risk Factor: Tumor Depth of Invasion

The next risk factor, tumor depth of invasion, is the risk factor most highly associated with recurrence and metastasis. It is defined by measurement in millimeters or tissue level of invasion. Tumors with the depth of invasion, measuring more than two millimeters, have a 10 times increased risk of local recurrence and the risk of metastasis increases with an increasing depth as well.

Slide 12 – Risk Factor: Lymphovascular Invasion

A final risk factor worth mentioning is lymphovascular invasion, which is when tumor invades vascular structures on histology. While it is a very aggressive finding, it is not included in the current staging systems, since it is very rare and studies have not been powered to detect its impact on outcomes.

Slide 13 – Primary Tumor Staging

I’m now going to move on to review different staging systems for primary tumors.


The current staging systems are based off of the risk factors we just reviewed. Over the coming slides, I’ll review three different systems. The first staging system is the AJCC Eighth Edition, which released an updated staging system for cutaneous squamous-cell carcinoma of the head and neck only. The staging system risk stratifies tumors by diameter with tumors less than 2 cm being stage T1 and tumors 2-4 cm being stage T2. T3 tumors require one of four criteria, either diameter greater than 4 cm, minor bone
erosion, perineural invasion of large-caliber nerves or depth of invasion beyond subcutaneous fat or at least six millimeters. T4 tumors are very rare and have a more significant bone invasion.

Slide 15 – Changes from AJCC 7th Edition

AJCC Eight differs from AJCC Seven in the following ways. Low-stage tumors are based on diameter alone and upstaging to T3 requires one of the four risk factors I just reviewed whereas previously, there needed to be bone invasion to be classified as T3. There is also a change in some of the risk factors. AJCC Eight no longer includes poorly differentiated histology or location as a risk factor. PNI of large-caliber nerves is required rather than of any nerve, which was what was included in AJCC Seventh Edition and depth of invasion is deeper for AJCC Eight.

The changes to AJCC Eight significantly improved risk stratification. Almost all the poor outcomes occurred in AJCC Seven T2 whereas the majority of outcomes are now captured in AJCC T3.

Slide 16 – Limitations to AJCC 8

However, while AJCC Eight is a drastic improvement to AJCC Seven, there are a few limitations. The first is that only one risk factor is required to upstage the T3, which means that a large number of tumors end up getting upstaged. Although this group does contain the majority of poor outcomes, the positive predictive value is low. The second problem is that it excludes poorly differentiated histology and the number of tumors that do not get upstaged, but develop a poor outcome happen to be poorly differentiated. The staging system is also limited to head and neck tumors. Although we can extrapolate to non-head and neck cases, it does not technically apply. Finally, one
of the major drawbacks is that there are equivalent risks for all poor outcomes in T2 and T3 tumors by AJCC Eight. There is a large heterogeneous group with a 13% risk of nodal metastasis and an 8% risk of death.

Slide 17 – Staging Systems: Brigham and Women’s Hospital (BWH)

Another staging system frequently used is the Brigham and Women's Hospital staging system. This system is built on four risk factors, including tumor diameter of two centimeter or more, poorly differentiated histology, perineural invasion of large-caliber nerves measuring 0.1 millimeters or greater, and tumor depth of invasion beyond fat, other than bone, which automatically upstages to T3. Tumors with zero risk factors are T1, one risk factor are T2, two to three risk factors are T2B, and all four risk factors or bone invasion are T3.

Slide 18 - AJCC 8 vs BWH Staging System

How does AJCC Eight compare to Brigham and Women's? Both high stages, i.e. AJCC Eight T3, or T4, and Brigham and Women's T2B and T3 capture similar number of outcomes. However, twice as many tumors are classified as high-stage by AJCC Eight. Thus, twice as many tumors would require additional staging or treatment if we use the high stages to risk-stratify tumors. In addition, if we look at the specificity of the two systems to detect nodal metastasis or disease-specific death, 93% of low-stage Brigham and Women tumors will never develop a poor outcome compared to 85% by AJCC Eight.

Slide 19 – Breuninger System for cSCC-specific Survival

There is one other system worth mentioning, which is the Breuninger system and is used to predict cSCC-specific survival. The staging system assigns points based on
depth, desmoplasia and immunosuppression. T1 tumors have zero or one point, T2 have two points, T3 have three points and T4 have four points.

**Slide 20 – Comparison of Staging Systems**

There was a recent paper that used a cohort out of Norway to compare the four primary tumor staging systems that I just reviewed, AJCC Seven, Eight, Brigham and Women's and the Breuninger system. The authors evaluated the sensitivity, specificity, correctly classified tumors, and the C-index. I want to focus on the C-index, which is the measure of the performance of a staging system. What we see is that Breuninger and Brigham and Women's both have a similar C-indices. You see that Breuninger has a C-index of 0.82 and Brigham has a C-index of 0.81. You may be wondering how we interpret this. A C-index of 0.7 means that the model is good and 0.8 means the model is strong. You may be wondering is strong good enough. We can put this into context. For lung and breast cancer, which are both well validated, well accepted staging systems, the C-index is 0.78 and 0.84 respectively. We see that both Breuninger and Brigham and Women's are very comparable. By using clinical and histologic risk factors, we were actually doing a pretty good job at risk-stratifying the tumors.

**Slide 21 – Nodal Staging**

I now want to move on to discuss nodal staging.

**Slide 22 – Regional Lymph Nodes**

There is a well-established nodal staging system included in AJCC Eight. The relevant factors for nodal staging system are number and size of lymph nodes and whether there is extracapsular extension of tumor. A single involved lymph node measuring less than or equal to 3 cm without extracapsular extension is classified as N1. There are three
categories within N2, all of which have no presence of extracapsular extension. N2A is a single lymph node greater than 3 cm, but less than 6 cm. N2B is the presence of multiple lymph nodes, less than or equal to 6 cm. N2C is when there is bilateral or contralateral lymph node involvement that are less than or equal to 6 cm. N3A is a single lymph node greater than 6 cm, but without extracapsular extension and finally, N3B is any lymph node with extracapsular extension.

Slide 23 - Defining Locally Advanced and Metastatic Disease Not Amenable to Surgery

The mainstay of treatment for primary cutaneous squamous-cell carcinomas, or those with nodal metastasis, is currently surgery, if possible, adjuvant therapy. However, there are a group of tumors that are not amenable to surgery and sometimes identifying locally advanced and metastatic squamous-cells is not straightforward.

Slide 24 – Locally Advanced/Unresectable

There is no solitary definition for locally advanced and unresectable squamous-cells. This is mostly due to the fact that there are a number of factors that are considered when evaluating whether a primary tumor is resectable.

The first is tumor location and whether a clear surgical margin can be obtained based on the extent of invasion and surrounding structures. Another factor in the same vein is the feasibility of a surgery. For example, a tumor that invades the skull with extension to the dura, may not be resectable if it approaches the sagittal sinus. In addition, patient comorbidities is a large consideration. If the tumor is invading the dura and does approach the sagittal sinus, but the patient cannot tolerate a free flap, then the tumor may also not be resectable. Finally, consideration of alternative treatment options is taken into account.
Slide 25 – Nodal Metastasis

Nodal metastasis is easier to define, but sometimes identifying inoperable patients is also not clear-cut. Currently, surgery plus radiation is the standard of care for metastatic squamous-cell carcinomas to the parotid or regional lymph nodes. The local regional recurrence rate is about 20% for such patients and five-year disease-free survival is about 73%. N1 tumors, i.e. solitary lymph nodes 3 cm or less in size without extracapsular extension, have an excellent prognosis with a 5% local regional recurrence rate and a five-year disease-specific survival of 100%. This highlights the importance of early diagnosis but again, not all nodal disease is operable. For example, those that wrap around neurovascular bundles may be deemed inoperable as well.

Slide 26 – Determining Whether A Tumor is Resectable

Each patient needs to be considered individually to determine whether a surgery can be curative or whether it is futile.

Slide 27 – Value of Multi-D Care

Since each tumor is so different, determining the best course of treatment for many aggressive or metastatic cutaneous squamous-cell carcinomas requires a multidisciplinary care team. This team often includes individuals from surgery, dermatology, radiation oncology and medical oncology to create an individualized treatment plan. In addition, many patients have multiple comorbidities. We often have to include other specialties, such as the transplant team to determine what is the best and safest treatment plan for each patient. In our clinic, our nurses are essential to the management as well and help to facilitate all various aspects of the care.

Slide 28 – Current Understanding of the Pathophysiology of Advanced/Metastatic cSCC
I want to end this portion of the lecture by discussing current understanding of the pathophysiology of advanced and metastatic squamous-cell carcinomas.

**Slide 29 – Mutational Burden of cSCC**

Squamous-cell carcinomas are very interesting, since they have the second greatest mutational burden compared to any other malignancy. The only other malignancy with a greater mutational burden is basal cell carcinoma, which has a 1.5 times greater mutational burden. To put it into further perspective, cutaneous squamous-cell carcinomas have five times more mutations than lung cancers and four times higher mutations than melanomas. This translates to many mutations, but the most common ones are found in P53 notch, CDKN2A, and RAS.

**Slide 30 - Future of Molecular Testing**

The future of cutaneous squamous-cell carcinoma risk stratification may include genetic studies in order to improve on our ability to identify those at risk for poor outcomes. However, due to the high mutational rate without a single candidate gene, future testing will need to be based on multiple genes. Interestingly, a predictive model for the risk of recurrence based on 73 candidate genes had a higher positive predictive value compared to the current anatomic and histologic derived staging systems.

**Slide 31 – PD-1/PD-L1 Pathway in Tumor Proliferation**

PD1 and PD-L1 expression has been shown to be extremely relevant in a number of cancers. To briefly review the pathway, T cells express PD1 receptor and binding of this receptor to PD-L1 on tumor cells results in downregulation of T cell effector functions that destroy tumor cells. PD1 antibody inhibitors block this pathway and allow T cells to maintain antitumor functions. PD1 and PD-L1 expression has been shown in cSCCs.
However, the relationship between expression and treatment response has yet to be defined.

With that, I’m going to turn the remainder of this talk over to Dr. Anne Silk who will discuss management of resectable and metastatic cutaneous squamous-cell carcinomas.

**Slide 32 - Management of Unresectable and Metastatic cSCC: Chemotherapy and EGFR-targeted Therapy**

**Ann Silk, MD:** Thank you, Dr. Ruiz. Prior to the availability of immunotherapy, treatment options for cutaneous squamous cell carcinoma were very limited. The two main systemic options were conventional, cytotoxic chemotherapy, and EGFR inhibitors. Before we discuss the data on immunotherapy, I think it’s useful to review some data on these two types of treatments as it highlights why immunotherapy is revolutionizing the treatment of unresectable and metastatic cutaneous squamous cell carcinoma.

**Slide 33 – Platinum-based Chemotherapy**

First, we will discuss platinum-based chemotherapy. Cutaneous squamous cell carcinoma and squamous cell carcinoma of the head and neck look very similar under the microscope. Because of the histological similarity, chemotherapy regimens used in head and neck cancer have been extrapolated and used in cutaneous squamous cell carcinoma. Cisplatin is the most active agent. It is the backbone of most combination regimens. The response rates are fairly good, ranging from 40% to 80%, but responses are generally not durable. Progression-free survival is generally about five and a half months and the overall survival is generally about 11 months.
There are no large randomized studies examining platinum-based chemotherapy for cutaneous squamous cell carcinoma. This study is a small study of 28 patients who were a mixture of locally-advanced, unresectable, and metastatic disease. The patients were treated with various regimens of platinum-based chemotherapy, taxanes, cetuximab or combination. Seventy-two percent of patients received platinum-based chemotherapy. A partial response was seen in 44% of patients and 24% had stable disease. No patients had a complete response. The median progression-free survival was 5.5 months. The three-year overall survival was only 22%.

Moving on to EGFR inhibitors, as EGFR protein overexpression, genetic amplifications, or mutations occur in multiple types of squamous cancer, EGFR is a rational therapeutic target in cutaneous squamous cell carcinoma. Cetuximab is a monoclonal antibody that has modest activity in cutaneous squamous cell carcinoma. In one small Phase II study of 36 patients, the response rate was 28%. The median PFS was only 4.1 months. The most frequent AE was a grade 1 to 2 acne-like rash, which occurred in 78% of patients. Panitumumab is another monoclonal antibody against EGFR with similar activity and a similar safety profile.

With regards to using chemotherapy and cetuximab in combinations, we again extrapolate from the head and neck literature. The addition of cetuximab to chemotherapy was found to improve survival in head and neck squamous cell carcinoma in the extreme study. This approach has been described in small studies in
cutaneous squamous cell carcinoma. In one study, locally-advanced cutaneous squamous cell carcinoma patients were treated with platinum plus 5FU plus cetuximab. Ninety-two percent became amenable to surgery. A complete response was achieved in 65%. Median overall survival was 26 months. In another study, cutaneous squamous cell carcinoma patients were treated with cetuximab or cetuximab plus carboplatin. In the whole study population, the response rate was 21%. The median overall survival was 9.5 months.

**Slide 37 – Articles**

Here is that study of 14 locally-advanced or metastatic cutaneous squamous cell carcinoma patients. Overall, three of the 14 patients had a partial response and six had stable disease. There were no complete responders. Median overall survival was less than 10 months and median progression-free survival was less than three months. The patients who received carboplatin plus cetuximab did somewhat better than those who received cetuximab alone with a median PFS of 5.2 versus 2.2 months.

**Slide 38 – Systemic Therapy + Radiation Therapy**

Systemic therapies have been used concurrently with radiation therapy to treat locally-advanced cutaneous squamous cell carcinoma. For locally-advanced non-metastatic patients, chemotherapy or cetuximab can be added to try to improve the effective radiation therapy. A few small studies of eight to 12 patients demonstrate the safety of cetuximab plus RT. The outcomes are similar to chemotherapy plus RT. Cetuximab is generally more tolerable. Cetuximab plus RT is a reasonable alternative to cisplatin for locally-advanced disease, especially in patients who are elderly or have poor renal function.
Slide 39 – Summary

To summarize this section, chemotherapy particularly cisplatin or platinum containing combinations with cetuximab can induce a response in cutaneous squamous cell carcinoma. Cetuximab has only modest activity as a single agent and radiation therapy can be combined with chemotherapy or cetuximab although radiation therapy plus cetuximab has better tolerance.

Slide 40 – Immunotherapy

Next, we will discuss immunotherapy using PD-1 immune checkpoint inhibitors.

Slide 41 – Early Reports of Activity of PD-1 Immune Check-point Inhibitors

In 2016 and 2017, the activity of PD-1 inhibitors began to emerge as a signal. A handful of case reports described cutaneous squamous cell carcinoma patients who were successfully treated with either nivolumab or pembrolizumab.

Slide 42 - Cemiplimab

Cemiplimab is a PD-1 blocking antibody, which was studied in unresectable, locally-advanced and metastatic cutaneous squamous cell carcinoma patients. In the pivotal trial, no prior therapy was required. Patients with chronic lymphocytic leukemia and other lymphomas were excluded. Patients with organ transplants or bone marrow transplant were also excluded from participation.

Slide 43 – Article

The published manuscript on cemiplimab includes both the expansion cohort of the Phase I study and the metastatic disease cohort of the Phase II study. I am going to review some of the important points of the study in the upcoming slides, but I will mention right away that the response rate in the two cohorts was about 50%. The
median follow-up time was 7.9 months in the Phase II metastatic cohort. At the time of data cutoff, 82% of responding patients continued to have a response. These results were published in June 2018, and cemiplimab received FDA approval in September 2018.

**Slide 44 – Baseline Characteristics of the Patients**

This table shows the baseline characteristics of the patients. The median age was 73 and 71 years old in the Phase I expansion and the Phase II metastatic disease cohorts, respectively. The head and neck was a predominant site of the primary tumor, accounting for 69% and 64% of the patients in each cohort.

I would like to point out the previous systemic therapy because more than half of patients had already received prior systemic therapy, and 82% had prior radiation therapy.

**Slide 45 – PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous Cell Carcinoma**

This waterfall plot shows the best tumor response for the patients in the Phase II study. All the bars below the X axis are target tumors that had a decrease in diameter from baseline. The brown bars indicate complete or partial response. The purple bars are stable disease. The green bars are progressive disease. You will note that we have a few green bars below the X axis. This indicates patients where the target tumor did respond, but the patient had progression of other non-target cutaneous squamous-cell carcinoma disease.

**Slide 46 – Efficacy of Cemiplimab**
Again, the activity of cemiplimab was very good. In the metastatic disease cohort with 75 patients, the response rate was 47%. In the locally advanced disease cohort with 33 patients, the response rate was 49%. Overall, 61% of responses were durable for more than six months.

Slide 47 – PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous Cell Carcinoma

This is the Kaplan-Meier plot of progression-free survival. I will mention that in the metastatic disease cohort of the Phase II study, the median progression-free survival had not been reached at the time of the data cutoff. The estimated probability of progression-free survival from baseline through 12 months was 53%.

Slide 48 – Adverse Events

Adverse events do occur. In the Phase II study, treatment-related adverse events that occurred in more than 10% of patients were fatigue, diarrhea, rash, and pruritis. Immune-mediated adverse reactions, including pneumonitis, colitis, hepatitis, nephritis, adrenal insufficiency, diabetes mellitus, hypo and hyperthyroidism, and infusion reactions were also reported. However, treatment discontinuation due to adverse events was reported in only 5% to 7% of patients.

Slide 49 – FDA Approved Cemiplimab

In late September 2018, the FDA approved cemiplimab. This is the first and only drug approved for this disease. The indication, specifically, is for patients with metastatic cutaneous squamous-cell carcinoma or locally advanced cutaneous squamous-cell carcinoma who are not candidates for curative surgery or curative radiation.

Slide 50 – Cemiplimab Administration
The recommended dose and schedule of cemiplimab per the FDA label is 350 milligrams IV over 30 minutes every three weeks. It is not adjusted for body weight. It is a flat dose.

**Slide 51 – Cemiplimab Responders**

Here are two examples from the paper published in the New England Journal of Medicine. The gentleman in the top panels had several large in-transit metastases spread across his scalp. After cemiplimab treatment, the nodules resolved. The gentleman in the lower panels has a large ulcerated cutaneous squamous-cell carcinoma in the posterior auricular area. After cemiplimab treatment, the ulcerated tumor has significantly shrunk and the ulcer is healing by secondary intent.

**Slide 52 – Patient Images**

This is a patient with metastatic cutaneous squamous-cell carcinoma. He has large tumors in the left supraclavicular area that are spreading across his chest and up the left side of his neck. He also had lung metastases. In the lower panel, you can see that his cutaneous metastases were melting away after two months of a PD-1 inhibitor. His response deepened over time. At one year, he achieved a complete response for his cutaneous disease, and he had 92% improvement in the lung metastases.

**Slide 53 – Biomarkers in Development**

With regard to biomarkers, there are no biomarkers that are proven to be helpful in selecting patients who will have a higher likelihood of response to cemiplimab, but in general, there are predictors that are being studied that may predict response to immune checkpoint inhibitors, including PD-L1 expression, tumor mutational burden, and the T-cell-inflamed gene-expression profile. In other cancers like lung and breast
cancer, percent PD-L1 expression in the tumor correlates somewhat with response to checkpoint inhibition.

**Slide 54 - PD-L1 expression in patients treated with cemiplimab; Tumor response pre ICR by PD-L1 status (LA Cohort)**

At the 2019 ASCO Annual Meeting, Dr. Migden presented an update on the cemiplimab study, including some biomarker data on the patients in the locally advanced cohort. The overall response rate, the ORR, was analyzed by PD-L1 expression less than 1% or greater than or equal to 1%. The response rates were 35.3% versus 54.8%. The 95% confidence intervals were overlapping, suggesting there was no significant difference. On the right side of the table, PD-L1 positive status was further subdivided by 1% to 5%, 5% to 50%, and 50% or more. Again, there was no clear difference in the response rates. It seems that PD-L1 expression is not predictive in locally advanced cutaneous squamous cell carcinoma.

**Slide 55 – Head and Neck Squamous Cell Carcinoma (HNSCC) – TMB and GEP**

What about tumor mutational burden and gene expression profiling? In head and neck squamous cell carcinoma, these are associated with response. In a pan-cancer study of patients who were treated with pembrolizumab, the responders in blue had, in general, higher tumor mutational burden and higher gene expression profile of T-cell inflammation markers than non-responders. This was true of all cancer studied in the left two panels and of head and neck squamous cell carcinoma in the right two panels.

**Slide 56 – TMB and GEP Are Independent Predictors for Response to PD-1 Antibody in HNSCC**
In the same study, tumor mutational burden and gene expression profile were found to be independent predictors in head and neck squamous cell carcinoma. Patients were divided by tumor mutational burden, high versus low, and gene expression profile, high versus low, in these graphics.

When both predictors are high, as in the pink boxes, the response rates are highest. When both predictors are low, as in the gray boxes, the response rates are low. In fact, there were zero out of 15 responses in head and neck squamous cell carcinoma patients. If either tumor mutational burden or gene expression profile is high, but not the other, the response rates are intermediate.

**Slide 57 – TMB May Be Predictive of Response to Cemiplimab**

Tumor mutational burden may also be predictive in cutaneous squamous cell carcinoma. At the 2019 ASCO Annual Meeting, Dr. Migden also presented tumor mutational burden data on the patients in the locally advanced cohort. Median tumor mutational burdens were 74.2 versus 28.7 mutations per megabase in the responders versus the non-responders. There is a slight trend indicating an association between clinical activity of cemiplimab and tumor mutational burden. Therefore, tumor mutational burden deserves further study as a biomarker in cutaneous squamous cell carcinoma. Unfortunately, no data on gene expression profile of the T-cell-inflamed signature were presented.

**Slide 58 – Biomarkers Summary**

In summary, there is no well-established biomarker for a response to immune checkpoint blockade in cutaneous squamous cell carcinoma. However, early results
indicate that PD-L1 expression does not appear to be predictive in this disease, and tumor mutational burden and gene expression profiling deserve further investigation.

Slide 59 – Special Populations: Immunosuppressed Patients

Immunosuppressed patients are a special population who deserve a mention. Solid organ and bone marrow transplant recipients are up to 70 times more likely to develop cutaneous squamous-cell carcinoma. As a first step, it is helpful to decrease immunosuppressive medications as much as possible. Because of a lower risk of skin cancer development, mTOR inhibitors are generally preferred over calcineurin inhibitors, such as tacrolimus. It is well known that anti-PD-1 agents may cause autoimmunity. The use of PD-1 inhibitors can cause acute rejection of the transplanted organ or can stimulate graft-versus-host disease. The frequency of rejection is not well known, but the chance is estimated to be up to 50%. In patients for whom that risk is unacceptable, particularly heart and lung transplant recipients, we must rely on the older therapies, including cetuximab, radiation therapy, or chemotherapy.

Slide 60 – Case Report

A successful case report was published in the New England Journal and serves as an instructive example in the absence of more definitive data. The authors described the treatment of a kidney transplant recipient who was treated for a small bowel cancer with nivolumab. His immunosuppressive regimen consisted of sirolimus and a specific tapering regimen of prednisone, wherein he took 40 milligrams daily of prednisone the week before the nivolumab infusion, then 20 milligrams the week following nivolumab. Then, 10 milligrams daily. The target range of sirolimus was also lowered during the week he received nivolumab. The patient’s cancer did not progress further. He did not
reject his kidney graft. No formal studies have been conducted in this population.

Oncologists must use their judgment to decide how to modify immunosuppression when PD-1 treatment is necessary.

Slide 61 – Future Directions

Cutaneous squamous-cell carcinoma is a very active field for research. There are multiple Phase II trials that are in progress or planned. There are trials in adjuvant treatment, trials in unresectable and metastatic disease. Intrallesional approaches are also under investigation. For transplant recipients, there is now a national study using combinations of ipilimumab, nivolumab, and tacrolimus for renal transplant subjects.

Slide 62 – Summary

To summarize the management of unresectable cutaneous squamous-cell carcinoma, multidisciplinary input is valuable for complex cases to make the optimal determination between local versus systemic therapy. Cemiplimab is indicated for patients with metastatic or locally advanced disease who are not candidates for curative surgery or curative radiation. Happily, cemiplimab has replaced chemotherapy for first-line therapy. Cemiplimab does not require any biomarker to treat.

For bone marrow transplant and solid organ transplant recipients, acute rejection may occur with anti-PD-1 therapy. We must use chemotherapy and cetuximab if the risks of rejection are unacceptable. The effects of anti-PD-1 are not known for patients with other forms of immunosuppression.

Slide 63 – Case Presentation

Now, we will discuss a case presentation. The woman pictured here has a 22-centimeter tumor, which she had neglected while caring for her sick husband. On MRI,
the tumor was abutting the spinous processes. On PET scan, she had no evidence of distant metastasis. Due to chronic bleeding from the tumor, her hemoglobin was four grams per deciliter at the time she presented. Her Brigham and Women’s Hospital stage is T3 because bone invasion automatically upstages the tumor to a T3, but she also has two other risk factors, which are diameter greater than two centimeters and poorly differentiated histology. What treatment would you recommend for this patient? Because of the size and the bone invasion, she was not a good candidate for curative surgery or curative radiation. Her treating physician recommended cemiplimab on a clinical trial.

**Slide 64 – Complete Response on Cemiplimab**

Her tumor responded to cemiplimab. After six cycles, she had a radiologic, histologic, and clinical complete response. She has now been off-treatment since November 2018. She continues to have no evidence of disease at this time.

**Slide 65 – Thank you**

That completes our activity for today. Thank you for joining us. To receive credit for viewing this program, you must complete the post-test and survey. While this only takes a few minutes, your feedback is very important to help us gauge the impact of this CME activity. Your responses also guide us in developing future educational programs targeted to your specific interest and addressing the clinical challenges you experience.