# A MULTIDISCIPLINARY EXPERT-DRIVEN CONSENSUS ON THE EVOLVING TREATMENT OF PATIENTS WITH ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA

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## BACKGROUND

- Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer, with an estimated annual incidence of ~700,000 in the US resulting in over 8000 deaths/year[1,2]
- Radiotherapy, chemotherapy, and targeted therapy are available for the management of advanced CSCC, defined as metastatic or locally advanced disease not amenable to surgery or radiation; however, there is a lack of randomized clinical trial data for these options and no standardized management approach[3,4]
- In addition to the medical burden of CSCC, patients suffer poor quality of life from functional loss, impairing surgeries, and the psychosocial impact of the disease[5,6]

## OBJECTIVE

- The aim of the EXCeL program was to help standardize patient characterization and develop evidence-based consensus statements for advanced CSCC with respect to tumor staging, work up, treatment and surveillance with the aim of providing up-to-date practical recommendations for physicians

## METHODS

- In October 2018, a multidisciplinary steering committee (SC) of experts in the field of advanced CSCC was convened (five dermatologists [including four Mohs surgeons], three medical oncologists, two head and neck surgeons, two radiation oncologists, and a patient)
- A modified Delphi process was used to develop consensus recommendations (Figure 1):
  1. Five key areas of focus were identified (diagnosis, staging systems and risk stratification, treatment modalities in advanced CSCC, referral patterns, and patient perspective)
  2. Fourteen key questions were developed, ranked and refined to identify clinical gaps. A final list of 12 questions were selected to develop consensus statements
  3. Ten bibliographic fellows performed a robust literature review to gather evidence and draft statements for each question (Figure 2). Statements were refined by the SC for consensus voting
  4. The SC refined and finalized recommendations during three online voting sessions

**Figure 1. Modified Delphi Process for the Consensus Process**


*Consensus was achieved if ≥75% of participants scored the recommendation within the 7–9 range and ≤25% scored it within the 1–3 range period

**Figure 2. Literature Research and Review Process**

- Databases included PubMed and Google Scholar
- Key abstracts from congresses were also included (e.g. from American Society of Clinical Oncology, the European Academy of Dermatology and Venereology, the American Academy of Dermatology, and the Society for Investigative Dermatology)

↓

5471 references were identified and screened

↓

161 references were used to develop final recommendations

## SELECT CONSENSUS STATEMENTS AND KEY RECOMMENDATIONS

### Identification, Staging, and Risk Stratification of Advanced CSCC

| Criteria for LA CSCC and metastatic CSCC | Consensus |
|---|---|
| • LA CSCC is a local tumor where surgery or radiation is unlikely to obtain clearance of the tumor, or where the patient is not a candidate for surgery or radiation due to an inability to safely reconstruct the wound, or due to high morbidity unacceptable to the patient | 82% |
| • Metastatic CSCC can be defined as disease that has spread from the original site to a distant organ or in subcutaneous tissues beyond the draining lymph nodes of the primary CSCC location<br>Note: In transit metastasis (biopsy proven CSCC in dermal and subcutaneous tissue in the area between the primary CSCC and its draining lymph nodes) is classified as LA disease | 87.5% |

| Criteria for 'non candidacy for surgery' for patients with advanced disease | Consensus |
|---|---|
| • Appropriateness for surgery can be best assessed by a surgeon including but not limited to Mohs surgeons, head and neck surgeons, and oncologic surgeons with experience treating patients with advanced CSCC. A multidisciplinary discussion of therapeutic options with oncologists, radiation oncologists, and patients' primary physicians can be helpful in weighing risks and benefits of various treatment approaches, also considering patient comorbidities. For complex cases second opinions are encouraged | 89% |
| • The appropriateness of resection should be discussed with the patient. This discussion should include the likelihood of tumor clearance with surgery and any significant risk of morbidity to determine whether the morbidity is acceptable to the patient | 89% |

| The use of different staging systems for the management of advanced CSCC[7,8] | Consensus |
|---|---|
| • The BWH T staging system may be used to estimate risk of recurrence and metastasis and identify patients who may benefit from radiologic nodal staging or increased surveillance for recurrence | 78% |
| • AJCC8 N2 identifies patients at increased risk of regional treatment failure after surgery +/ radiation. These patients may benefit from consideration of systemic therapy if such failure occurs or the nodal disease is inoperable | |
| • Metastases to distant organs identifies patients in need of systemic therapy | |
| • Based on the current evidence, tumor (T) staging does not have a prominent role in determining appropriateness for systemic therapy including immunotherapy in patients with advanced CSCC. However, nodal (N) and metastasis (M) staging systems do play a role | 78% |

| Synoptic pathology for CSCC should include the following minimum key requirements | Consensus |
|---|---|
| • Clinical preoperative tumor diameter (provided to the pathologist by the surgeon) | 89% |
| • Millimeter thickness OR tissue level of invasion | |
| • Millimeter depth measured from the granular layer of adjacent normal epidermis to base of tumor (Breslow thickness) | |
| • Tissue level depth of tumor invasion (e.g. dermis, fat, fascia) | |
| • Tumor differentiation (well, moderate, poor, undifferentiated) | |
| • Desmoplasia | |
| • Perineural invasion (PNI)<br>- Nerve caliber ≥0.1 mm OR<br>- Invasion of a nerve lying deep to dermis | |
| • Extent of lymphocyte infiltration (immunoscore) | |
| • Lymphovascular invasion | |
| • Specify if the tumor may represent a metastasis | |

| Patient/tumor characteristics suggesting increased risk for recurrence and/or metastatic disease | Consensus |
|---|---|
| • Tumor diameter ≥2 cm, presence of desmoplasia, tumor thickness (Breslow thickness), tissue level of invasion, caliber of perineural invasion, bone erosion and poor differentiation are independent risk factors for local recurrence, metastasis, and/or death from disease in patients with CSCC | 89% |

| Supplemental tests to identify tumor characteristics suggestive of increased risk for recurrence and/or metastatic disease | Consensus |
|---|---|
| • Molecular tests are being investigated and should not be used to make treatment decisions. Future development of molecular staging tests may provide better risk stratification. However, until more conclusive evidence is available, molecular tests should not be used to guide treatment or referral decisions | 100% |

### Considerations for the Management of Advanced CSCC

| Radiation therapy for advanced CSCC may be considered in the following settings | Consensus |
|---|---|
| • Adjuvant radiation therapy may be considered in patients with uncertain surgical margins (e.g. multifocal or large caliber nerve invasion, or lymphovascular invasion) or with a recurrent tumor. Adjuvant radiation was associated with a lower risk of local recurrence in primary tumors with large caliber (>0.1 mm) nerve invasion in a single study | 75% |
| • Definitive radiation therapy versus systemic therapy may be considered when gross disease is present and is not amenable to surgical resection. However, efficacy of radiation has not been investigated in grossly unresectable CSCC<br>- Imaging is strongly suggested when clinical evaluation for assessment of response is insufficient following definitive radiation therapy. Imaging modalities may include CT, PET, PET/CT, MRI, and ultrasound and should be selected based on clinical information and available evidence | |
| • Adjuvant radiation may be considered for local control of microscopic residual disease that cannot be surgically resected<br>Note: Given the approval of cemiplimab, the curative confidence and morbidity of definitive, single modality radiation therapy should be considered, discussed with the patient, and weighed against systemic options such as immunotherapy | |

| Immunotherapy in the management of advanced CSCC | Consensus |
|---|---|
| • Cemiplimab is the only FDA approved therapy for use in patients with LA or metastatic CSCC who are not candidates for curative surgery or curative radiation. The approval was based on Phase I/II data. Cemiplimab should be used as first line therapy in patients requiring systemic treatment | 87.5% |
| • Appropriate use of cemiplimab in immunosuppressed patients has not been established as they have been excluded from trials published so far. However, cemiplimab treatment is not necessarily precluded in these patients | 87.5% |
| • Treatment decisions should weigh the risk of death and disability from the tumor versus the risk of immunotherapy, which can provoke exacerbations of autoimmune conditions (e.g. lupus, colitis) and organ rejection in organ transplant recipients, which can lead to rapid death in patients with lung, heart, and liver transplant | 87.5% |
| • In the neoadjuvant and adjuvant settings, treatment of CSCC with immunotherapy is under investigation via clinical trials. Enrollment of eligible patients in these trials is strongly encouraged | 100% |

| Chemotherapy or targeted therapy for the management of advanced CSCC | Consensus |
|---|---|
| • Chemotherapy or targeted therapy can be considered in patients who are not candidates for immunotherapy, who have progressed on immunotherapy, or who cannot tolerate immunotherapy related adverse events. However, response rates are low and generally of short duration. The adverse event profile may be more serious, depending on the choice of therapy | 87.5% |
| • Currently, there is no standard of care for neoadjuvant or adjuvant systemic therapy in advanced CSCC. In patients with LA and metastatic CSCC, immunotherapy should be considered first line, followed by targeted therapy and/or chemotherapy | 75% |

| Involving multidisciplinary team in patient care | Consensus |
|---|---|
| • Patients with LA or metastatic CSCC may benefit from an MDT discussion including experts in CSCC from the areas of surgery, medicine, and radiation. Such experts include (but are not limited to) medical oncologists, dermatologists/dermato oncologists, surgical oncologists (including head and neck and Mohs surgeons), and radiation oncologists | 100% |

## CONCLUSIONS

- Currently, there is no standardized approach for the diagnosis and management of advanced CSCC
- Immunotherapy should be considered first-line systemic therapy, following its recent introduction into the treatment paradigm
  - Additional studies are needed on immunotherapy in immunosuppressed patients, and in combination with other treatment modalities
- MDT discussion may be useful at key decision points or where additional specialist input is needed. MDT recommendations should be discussed with the patient
- Further research is needed in several areas (e.g. the role of curative radiation therapy, combination therapies, and the validation of biomarkers)
- The EXCeL consensus program outputs may provide physicians with practical recommendations to optimize outcomes for patients with advanced CSCC

### AUTHOR DISCLOSURE

**G Rabinowits:** reports consulting/advisory relationship and scientific advisory boards with Castle Biosciences, EMD Serono, Merck, Pfizer,Regeneron Pharmaceuticals, and Sanofi Genzyme. Additionally, he holds Regeneron Pharmaceuticals and Syros Pharmaceuticals shares; **MR Migden**: reports honoraria from Eli Lilly, Novartis, Regeneron Pharmaceuticals, institutional research funding from Genentech, Sun Pharmaceutical Industries Limited, and Sanofi Genzyme; **TE Schlesinger**: reports research funding from AbbVie, Aclaris, Allergan, BMI, Biofrontera, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, Kiniksa, Merz, Novartis, Pfizer, and Sisaf; honoraria and consulting/advisory relationship from/with Aclaris, Allergan, Almirall, Dermira, Ortho, Regeneron Pharmaceuticals, Sanofi Genzyme, and Sun Pharmaceutical Industries Limited; **CD Schmults**: reports consultant fees and grant research funding from Castle Biosciences and Regeneron Pharmaceuticals; research funding from Novartis; **RL Ferris**: reports honoraria from Amgen, Bain Capital Life Sciences, EMD Serono, GlaxoSmithKline, Iovance, Biotherapeutics, Eli Lilly,Numab Therapeutics AG, Oncorus, Ono Pharmaceutical, Pfizer, PPD, Regeneron Pharmaceuticals, TTMS, and Venti Rx Pharmaceuticals; research funding and honoraria from AstraZeneca/MedImmune, Bristol-Myers Squibb, Merck, and Tesaro; **M Freeman**: reports scientific advisory board and consultant fees with/from Regeneron Pharmaceuticals and Sanofi Genzyme; speaker for Regeneron Pharmaceuticals; **V Guild**: no disclosures; **S Koyfman**: reports research funding from Merck; **AC Pavlick**: reports consulting/advisory relationship, scientific advisory boards, and research funding with/from Regeneron Pharmaceuticals and Sanofi Genzyme; **N Swanson**: reports consulting/advisory relationship with Genentech, Regeneron Pharmaceuticals, and Sanofi Genzyme; **GT Wolf**: reports honoraria from Merck and Regeneron Pharmaceuticals; research funding from Brooklyn Immunotherapeutics; **SM Dinehart**: reports consulting/advisory relationship and scientific advisory boards with Regeneron Pharmaceuticals and Sanofi Genzyme; consulting/advisory relationship with Genentech; scientific advisory boards with Verrica Pharmaceuticals.

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