

ADVANCED CSCC POCKET GUIDE

WHEN SYSTEMIC THERAPY IS AN OPTION

A Quick Reference for Clinicians



Risk Factors for Local Recurrence or Metastases



HIGH RISK

- ✓ Any tumor on head/face/neck, hands/feet, pretibial, or anogenital area
- ✓ 2 cm to ≤4 cm on trunk/extremities
- ✓ Poorly defined borders
- ✓ Recurrent
- ✓ Immunosuppression (ie, SOTR)
- ✓ Site of prior RT or chronic inflammation
- ✓ Rapid growth tumor
- ✓ Neurologic symptoms
- ✓ Adenosquamous or sarcomatoid subtypes in any portion of the tumor
- ✓ Depth: 2 mm to 6mm and no invasion beyond SQ fat
- ✓ PNI

VERY HIGH RISK

- ✓ >4 cm (any location)
- ✓ Poorly differentiated
- ✓ Adenosquamous or sarcomatoid subtypes in any portion of the tumor
- ✓ Depth: >6 mm or invasion beyond SQ fat
- ✓ PNI: deeper than the dermis or ≥0.1 mm
- ✓ Lymphatic or vascular involvement

NCCN Guidelines® stratify into Low Risk, High Risk, and Very High Risk groups

High Risk and Very High Risk groups are associated with varying risk of local recurrence and metastasis

Once Very High-Risk Criteria Are Met: ACT



Consider imaging (CT/PET-CT) for nodal or deep-tissue involvement in higher-stage disease



Consider systemic immunotherapy (anti-PD-1) for locally advanced or metastatic disease not curable by surgery or radiation



Do NOT manage very high-risk disease with surgery alone—this is the referral trigger



Collaborate with a multidisciplinary team—Mohs/dermatologic surgery, radiation oncology, and medical oncology, as indicated

When to Refer



High/Very high-risk tumor features: ≥2 cm, invasion beyond fat or >6 mm depth, poor differentiation, PNI (≥0.1 mm), or LVI



Advanced stage: BWH T2b/T3 or AJCC-8 T3/T4—highest risk of metastasis and death



High-risk host factors: immunosuppression or SOTR; rapidly growing, recurrent, or in-transit disease



Not curable by surgery/RT: locally advanced or metastatic disease—candidate for systemic ICI



Adjuvant candidate (NEW): resected very high-risk CSCC after surgery + RT—Category 1 for adjuvant cemiplimab



Any node-positive disease: regional nodal involvement warrants tumor board input

When to Consider Immunotherapy for Advanced CSCC



Very high-risk CSCC with significant risk of extensive local recurrence, nodal, or in-transit metastasis

laCSCC that is primary or recurrent extensive disease, for which surgery and/or RT may not result in a cure or would possibly produce a significant functional impairment

Consider **neoadjuvant** therapy with cemiplimab if:

- » Nonreactive non-keratoacanthomatous rapid growth tumors
- » In-transit metastasis
- » Borderline resectable
- » Surgery alone may not be curative or may result in significant functional limitation

Consider **adjuvant** therapy with cemiplimab following adjuvant RT in patients with extremely high-risk nodal and non-nodal features

Surgical Candidates:

Consider **neoadjuvant** therapy with cemiplimab and/or clinical trial after multidisciplinary discussion

Nonsurgical Candidates:

Consider RT ± systemic therapy or systemic therapy alone if curative RT not feasible

FDA-Approved ICIs for Advanced CSCC

	Cemiplimab-rwl	Pembrolizumab	Cosibelimab-ipdl
Target/Class	Anti-PD-1/Human IgG4 mAb	Anti-PD-1/Humanized IgG4 mAb	Anti-PD-1/Human IgG4 mAb
CSCC Indication	» Adults with m/laCSCC who are not candidates for curative surgery or RT » For the adjuvant treatment of adult patients with CSCC at high risk of recurrence after surgery + RT (Oct 2025)	Adults with recurrent or m/laCSCC who are not candidates for curative surgery or RT	Adults with m/laCSCC who are not candidates for curative surgery or RT
Monitoring	Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment		