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Immunotherapy for early-stage cutaneous squamous cell carcinoma

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ABSTRACT

Cutaneous squamous cell carcinoma (CSCC) is a highly prevalent malignancy with rising incidence, particularly among elderly and immunosuppressed individuals. Although most early-stage cases are cured with surgery, a relevant minority present with high-risk features or anatomically complex disease. Immune checkpoint inhibitors (ICIs) have transformed the management of advanced CSCC and are increasingly being evaluated in perioperative settings. This review critically examines current evidence for adjuvant and neoadjuvant immunotherapy in resectable CSCC. Neoadjuvant ICIs studies, including cemiplimab, pembrolizumab, and nivolumab±ipilimumab, have reported consistent and striking rates of major and complete pathologic responses, frequently exceeding 50% and accompanied by opportunities for surgical or radiotherapy de-escalation. In contrast, adjuvant anti-PD-1 trials have produced divergent results: KEYNOTE-630 was negative, while C-POST improved disease-free, but not overall survival. These discrepancies highlight persistent limitations in risk stratification, since commonly used staging systems (American Joint Committee on Cancer, Brigham and Women's Hospital, Salamanca) insufficiently reflect disease biology and fail to incorporate immunosuppression, functional outcomes, or extent of planned surgery. Furthermore, the generalizability of current evidence is constrained by the exclusion of immunosuppressed populations and by rigid trial protocols that often mandate multimodal treatment, irrespective of biological sensitivity. Such 'one-size-fits-all' approaches miss critical opportunities for organ preservation and de-escalation. The future of early CSCC management lies in response-adapted strategies to tailor the extent of surgery, radiation, and systemic therapy. Next-generation studies must embrace biomarker-driven designs and broader inclusion criteria, approaching CSCC as a unique biological entity that demands a precision-medicine framework.

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INTRODUCTION

Cutaneous squamous cell carcinoma (CSCC) is the second most common form of skin cancer worldwide (second to basal cell carcinoma), with rapidly increasing incidence rates driven by cumulative UV exposure and aging, with individuals over 65 years accounting for approximately 70% of cases.[1 2] Immunosuppressed patients represent a distinct high-risk group: organ transplant recipients (OTR) have a 65-fold to 250-fold increased risk of developing CSCC compared with the general population, with more aggressive disease behavior and poorer outcomes.[3 4] CSCC is also the most common post-transplant malignancy, affecting up to 40% of OTR within 10 years.[5]

The socioeconomic burden of CSCC is substantial, exceeding US$4.8 billion annually in the USA and €5.2 billion in Europe, and this is particularly pronounced in immunosuppressed individuals due to multiple primaries, frequent recurrences, and intensive surveillance needs.[6–8]

Immune checkpoint inhibitors (ICIs) have revolutionized the management of advanced CSCC, achieving response rates >50% with rapid, durable benefit in many patients, including those who are elderly or frail.[9–13] These results have naturally prompted interest in moving immunotherapy into earlier disease stages, where the opportunity for cure—or prevention of progression—may be even greater.[14]

However, clinicians face several dilemmas in early-stage CSCC. Tumors often arise in anatomically complex head and neck regions, where radical surgery and adjuvant radiotherapy (RT) can lead to major functional and cosmetic morbidity. Additionally, many patients are immunosuppressed and systematically excluded from clinical trials, creating a major evidence gap. Key unanswered questions include whether to pursue maximal local control with surgery and RT, reserving systemic therapy for recurrence, or whether a brief neoadjuvant course of ICIs could reduce treatment morbidity in selected patients.[15]

Early neoadjuvant studies have indeed shown compelling pathological and clinical responses, occasionally enabling surgical de-escalation or omission,[14 16–22] although optimal integration with surgery and RT—including timing, number of cycles, and post-operative management—remains undefined.

Box 1 Key challenges in early-stage cutaneous squamous cell carcinoma (CSCC)

Inconsistent and suboptimal risk stratification
- ⇒ Current staging systems (American Joint Committee on Cancer, Brigham and Women's Hospital (BWH), Union for International Cancer Control) define 'high-risk' disease in divergent ways.
- ⇒ These frameworks show only moderate prognostic accuracy and often omit relevant variables such as immunosuppression, anatomical site, growth kinetics, and tumor biology.
- ⇒ Lack of harmonization directly impairs patient selection for perioperative trials.

Heterogeneous definitions of 'high-risk' across clinical trials
- ⇒ Neoadjuvant and adjuvant studies use disparate eligibility criteria (T3/T4 classification, multiple BWH features, node-positive disease, metabolic activity), producing non-comparable populations.
- ⇒ This heterogeneity weakens interpretation of outcomes and inflates perceived benefit.

Uncertainty around the role of surgery and adjuvant therapy after neoadjuvant response
- ⇒ Many protocols mandate surgery and/or one year of adjuvant PD-1 therapy irrespective of response.
- ⇒ Conversely, emerging response-adapted designs allow omission of surgery or radiotherapy in selected cases.
- ⇒ Lack of consensus undermines trial comparability and real-world applicability.

Suboptimal endpoints for neoadjuvant CSCC trials
- ⇒ Disease-free survival and recurrence-free survival depend on surgery being performed and do not capture critical preoperative events (progression during neoadjuvant therapy, failure to reach surgery).
- ⇒ Radiological response correlates poorly with pathological response, limiting its utility as a surrogate endpoint.

Risk of overtreatment in an elderly, comorbid population
- ⇒ Many patients included in perioperative trials may have modest true recurrence risk.
- ⇒ A year of adjuvant immunotherapy may expose frail individuals to unnecessary toxicity without proven benefit.
- ⇒ Trial designs derived from melanoma are often misaligned with CSCC biology and patient demographics.

Overall, these limitations demonstrate that early-stage CSCC requires disease-specific, biology-driven approaches rather than frameworks inherited from melanoma or mucosal SCC.

Compounding these uncertainties, current staging systems and high-risk definitions, largely developed in the preimmunotherapy era, are poorly aligned with the current clinical needs and remain inconsistent across guidelines and trials.[23] As a result, early, high-risk CSCC management is shaped by three main challenges: (1) risk stratification remains 'one-size-fits-all', with 3%–8% recurrence even in apparently low-risk disease[24]; (2) a small but clinically relevant proportion of patients (≈5%) will develop locally advanced or metastatic disease, yet we lack robust tools to identify them upfront[25]; and (3) the advent of immunotherapy has created new uncertainties around patient selection and treatment sequencing. These key issues are summarized in box 1 for reference.

In this Review, we critically examine the limitations of existing staging systems, synthesize evidence from neoadjuvant and adjuvant immunotherapy trials, and outline a clinically and biologically informed, response-adapted framework for early-stage CSCC. We also propose methodological priorities to improve trial design and clinical decision-making.

Current staging systems and high-risk criteria in CSCC

The staging of CSCC represents a critical step in patient management, directly influencing treatment decisions and prognosis. Several staging systems have been proposed, each attempting to refine risk stratification for better prognostication and therapeutic decision-making. Table 1 provides a comprehensive comparison of these staging systems, outlining their respective high-risk criteria and limitations. While each system offers unique advantages, no single model achieves optimal risk stratification. Given these limitations, an integrated approach combining multiple staging frameworks is often necessary to guide clinical management effectively. These inconsistencies are not merely theoretical: they have had direct consequences on the design of recent neoadjuvant and adjuvant immunotherapy trials. Each study has operationalized 'high-risk' disease using different—and often restrictive—criteria, reflecting the absence of a unified risk-stratification framework. For example, the neoadjuvant pembrolizumab trial (NCT04808999) required American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) T3 or T2 with ≥2 Brigham and Women's Hospital (BWH) high-risk features, whereas NEO-CESQ (NCT04632433) limited inclusion to stage III/IV (M0) disease, and the Australian De-Squamate study (NCT05025813) accepted stage II–IV M0 but relied heavily on imaging and metabolic responses to define 'high-risk' operability and eligibility.[19 22 26]

Similarly, the phase 2/3 adjuvant trials adopted heterogeneous definitions of 'high-risk resected disease',[27 28] making cross-trial comparisons challenging and highlighting the absence of a staging system truly tailored to CSCC biology (see tables 2 and 3).

The AJCC eighth edition, the BWH tumor classification system, and the UICC eighth edition remain the most commonly used. However, additional models, such as the Salamanca refinement of the AJCC eighth edition, and the updated National Comprehensive Cancer Network (NCCN) guidelines, have sought to address limitations inherent in these traditional frameworks.

The AJCC eighth edition is the most widely adopted system, providing a TNM-based approach that incorporates tumor size, perineural invasion (PNI), depth of invasion, and bone invasion.[29] It is important to note that this edition applies only to CSCCs of the head and neck, excluding lesions in other anatomical locations. While it serves as a standardized classification, its ability to stratify patients with intermediate-risk tumors remains limited, particularly within the T2 category. The UICC system, largely overlapping with the AJCC, provides

Table 1 Tumor staging and main risk factors in cutaneous squamous cell carcinoma (CSCC)

Staging system	Scope	Main criteria	Nodal staging included	ITMs included	High-risk location included	T definition clarity	Immuno suppression included	Use in clinical trials and limitations
AJCC 8th[29]	Full TNM (T/N/M)	Tumor size, depth of invasion, PNI, bone invasion (location indirectly via exceptions like ear, lip)	Yes	No	Ear, non-hair-bearing lip (if >2 cm triggers T2)	Moderate—overlap in T2 category; exceptions by location	No	Common use in clinical trials; limited stratification in T2; includes head and neck CSCC only; does not systematically reflect immunosuppression or anatomic risk
UICC 8th[56]	Full TNM (T/N/M)	Tumor size, deep invasion, nodal involvement	Yes	No	Not specified	Moderate—subcategories (a–d) unclear in practice	No	Overlaps with AJCC; lacks granularity
BWH[23 30]	T classification only	Tumor size, PNI, differentiation, depth beyond fat	No	No	Not specified	High—simple, risk-factor based	No	No N or M staging; not designed for full disease extent
Breuninger[57]	T classification only	Tumor thickness, immune status, differentiation	No	No	Ear	Moderate—requires pathology detail	Yes	Limited validation; omits N staging
Tübingen[58]	T classification only	Tumor thickness, differentiation, location (ear)	No	No	Ear	Moderate—lacks external validation	No	Limited validation; omits N staging
Salamanca refinement[59]	Primarily T; prognostic focus	Tumor size, depth, PNI, LVI, lymphatic invasion	Limited	No	Not clearly specified	High—improved stratification	No	Emerging use in clinical trials; unclear integration of anatomical risk; limited external validation
NCCN[35]	Risk stratification model (not full TNM)	Tumor size, PNI (symptomatic), LVI, growth rate, location, immunosuppression	No	No	Yes: head, neck, hands, feet, pretibia, anogenital	High—used for treatment decision-making	Yes	Not a formal staging system; not universally adopted

This table provides a comprehensive comparison of the major staging systems for CSCC. Each system is assessed based on its main criteria, definition and risk factors, tumor locations considered high risk, limitations, and clinical utility.
AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; LVI, lymphovascular invasion; NCCN, National Comprehensive Cancer Network; PNI, perineural invasion; TNM, tumor, node, metastasis; UICC, Union for International Cancer Control.

Table 2 Comparison of the phase III randomized trials C-POST (cemiplimab) and KEYNOTE-630 (pembrolizumab) in resected high-risk cutaneous squamous cell carcinoma

Feature	C-POST (NCT03969004) Cemiplimab[27]	KEYNOTE-630 (NCT03833167) Pembrolizumab[28]
High-risk definition	► ECE +≥1 LN >2 cm ► ≥3 positive LNs ► T4 with cortical bone/skull base invasion ► Clinical/radiologic PNI of named nerves ► Recurrent disease ► In-transit metastasis	► ECE +≥1 LN >2 cm ► ≥2 positive LNs ► T4 with cortical bone/skull base invasion ► Index tumor with ≥2 of: ► ≥4 cm+depth >6 mm or invasion beyond fat ► Microscopic PNI (multifocal <0.1 mm or single ≥0.1 mm) ► Poor differentiation/sarcomatoid ► Recurrence within 3 years ► Satellites±in-transit metastasis ► Lymphovascular invasion
Interval from RT to randomization	2–10 weeks	4–16 weeks
Treatment	Cemiplimab 350 mg vs Placebo Q3W×12 wks, then 700 mg Q6W for up to 36 wks (≤48 wks total)	Pembrolizumab 400 mg vs Placebo Q6W (≤54 wks total)
Median follow-up	24 months	28.6 months
Primary endpoint	DFS	RFS
24-month results	DFS: 87% vs 64% HR 0.32, p<0.001	RFS: 78% vs 69% HR 0.76, p=0.072
OS (24 months)	95% vs 92% HR 0.86	87% vs 91% HR 1.47
Grade 3/4 adverse events	15% vs 7%	26% vs 17%
Treatment-related deaths	1 cemiplimab-related myositis/myocarditis	0

DFS, disease-free survival; ECE, extracapsular extension; LN, lymph node; OS, overall survival; PNI, perineural invasion; Q3W, every 3 weeks; Q6W, every 6 weeks; RFS, recurrence-free survival; RT, radiotherapy.

further subclassification but faces similar challenges in risk differentiation.[30] Both systems suffer from limited distinctiveness, particularly in the T2 subgroup, meaning that patients within the same stage can have different outcomes.

The BWH system was designed primarily as a prognostic tool for predicting the occurrence of nodal metastases rather than a full TNM staging system.[23] It focuses on identifying patients at high risk of disease recurrence by integrating risk factors such as tumor size, differentiation, PNI, and depth beyond subcutaneous fat. Studies have demonstrated that BWH staging provides superior risk stratification compared with AJCC, particularly in distinguishing T2 lesions with a significantly increased likelihood of nodal involvement.[30] This system exhibits high distinctiveness and high homogeneity, particularly for identifying high-risk T2 lesions, but lacks nodal and metastatic staging.[23 30] As it does not incorporate nodal (N) or metastatic (M) staging, it is often used in conjunction with the AJCC/UICC systems in clinical practice.

One major limitation across these staging systems is the lack of a clear definition and incorporation of in-transit disease, which remains poorly categorized. Additionally, there is inconsistency in the assessment of nodal involvement, particularly in differentiating between microscopic and macroscopic involvement. The absence of a precise classification for these variables lowers the chance of an accurate prognostication and treatment decision-making.

Given the increasing number of clinical trials focusing on early-stage CSCC, it is crucial to develop a staging system that accurately reflects the true risk of local recurrence, distant metastasis, and disease-specific mortality. Consistent staging and risk stratification are critical for patients, clinicians, and for the interpretation of intervention studies (see tables 2 and 3). Future staging models should ensure clarity in T categorization, acknowledge the impact of high-risk anatomical sites, and incorporate patient-related factors such as immunosuppression status to improve prognostic accuracy.

Refining staging criteria to align with evolving treatment paradigms and incorporating molecular and immunological biomarkers will be essential for enhancing the precision of prognostication and optimizing therapeutic strategies for patients with CSCC. Notably, even recent randomized trials such as C-POST have based their risk estimates on historical data from the TROG 05.01 study, which evaluated concurrent chemoradiation versus RT alone in a highly selected population with head and neck CSCC, thus highlighting the current limitations in robust, contemporary prognostic models.[27 31]

Table 3 Summary of key results of the major neoadjuvant clinical trials in cutaneous squamous cell carcinoma

Study (NCT ID)	No of Patients	Design and inclusion criteria	Neoadjuvant therapy	Major pathologic response (MPR) (pCR)	Mandatory surgery	Adjuvant therapy	Median follow-up (months)	EFS/RFS
Ferrarotto *et al*, 2021 (NCT03565783)[16 17]	20	Phase 2, single arm Stage III–IVA of the Head and Neck	Cemiplimab 2 doses (6 weeks)	75% (55%)	Yes	Not mandated; (Chemo)-RT	42.3	3-year EFS 83.9 (all pt) 93% (MPR) 40% (non-MPR)
Gross *et al*, 2022 Update 2023, 2024 (NCT04154943)[14 18 60]	79	Phase 2, single arm Stage II-IV (M0)	Cemiplimab Up to 4 doses (12 weeks)	64% (51%)	Yes (extent adapted to response)	Not mandated; Cemiplimab (up to 48 weeks), RT	29.4	24-month EFS 86% (all pt) 92% (pCR) 89% (MPR) 64% (non-responders)
MATISSE (NCT04620200)[20 38]	50	Phase 2, randomized Stage T1-4 N0-3 M0 or TxN1-3 M0 and an indication for extensive and/or mutilating surgery	A: Nivolumab; B: Nivolumab+low dose Ipilimumab 2 doses (6 weeks)	A: 40%, B: 53% (pCR not reported)	No (20% declined surgery)	Not mandated; RT when indicated per guidelines (omitted in pCR)	31	12-month RFS 100% (MPR+cCR) 86% (pPR) 71% (pNR+cNR)
De-Squamate (NCT05025813)[21 26]	27	Phase 2, single arm Stage II-IV (M0), resectable, immunocompetent	Pembrolizumab 4 doses (12 weeks)	15% (15%), 48% CCR	No	Mandatory; Pembrolizumab up to 13 cycles, RT	18	EFS 74% (all pts) 94% (cpCR) 40% (non-cpCR)
Amatore *et al* 2024 (NCT04808999)[19]	30	Phase 2, single arm AJCC/UICC Stage ≥T3 (or T2 with ≥2 BWH high-risk features) and/or N+	Pembrolizumab 2 doses (6 weeks)	65% (57%)	Yes	Mandatory; Pembrolizumab up to 15 cycles	NA	NA
NEO-CESQ (NCT04632433)[22]	23	Phase 2, single arm Stage III/IV (M0) resectable high-risk	Cemiplimab 2 doses (6 weeks)	48% (39%)	Yes	Mandatory; Cemiplimab (1 year)	NA	NA

AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; cCR, clinical complete response; EFS, event-free survival; NA, not available; pCR, pathological complete response; RFS, recurrence-free survival; RT, radiotherapy; UICC, Union for International Cancer Control.

ICIs for the treatment of CSCC

ICIs have transformed the management of advanced CSCC, offering deep, rapid, and durable responses in a disease traditionally treated with a combination of palliative surgery, RT, or chemotherapy.[15]

The efficacy of ICIs in advanced CSCC has been demonstrated in pivotal trials. The phase 2 EMPOWER-CSCC-1 study demonstrated the efficacy of cemiplimab in patients with metastatic or locally advanced CSCC not eligible for curative surgery or RT, achieving a response rate of 47% with cemiplimab in patients with advanced disease, with a median time to response of 1.9 months and a durable disease control rate of 61%.[32] Similarly, in the phase 1 expansion cohorts, response rates reached 50%.[32] Similar response rates were observed in earlier phase 1 expansion cohorts, with clinical benefit irrespective of metastatic site. Based on these data, cemiplimab was approved as the standard of care in patients with advanced CSCC who are not candidates for definitive local therapy (ie, surgery or RT).

The KEYNOTE-629 trial further corroborated the efficacy of anti-PD-1 therapy in advanced CSCC. In this phase 2 study, pembrolizumab achieved a response rate of 34% in recurrent/metastatic or unresectable locally advanced disease, with durable responses in a substantial subset of patients with recurrent or unresectable locally advanced disease.[33] These results further validated PD-1 blockade as a cornerstone treatment in the advanced setting.

Beyond tumor response, cemiplimab has also shown a positive impact on health-related quality of life. In a post hoc analysis of EMPOWER-CSCC-1, patients experienced a clinically meaningful reduction in pain, with 43% reporting ≥10-point improvement by cycle 5, and over 80% showing maintenance or improvement across physical, emotional, and social functioning domains.[34] These findings underscore the capacity of PD-1 inhibition to not only prolong disease control but also preserve function and well-being in a vulnerable population.

Taken together, the robust efficacy of anti-PD-1 therapy in advanced CSCC has catalyzed its integration into earlier disease settings. Adjuvant cemiplimab has recently established a new standard of care for high-risk resected disease following regulatory approvals based on phase 3 evidence, whereas neoadjuvant strategies remain under active investigation to facilitate organ preservation and surgical de-escalation. Currently, neoadjuvant ICIs are not recommended for routine early-stage disease; however, current NCCN guidelines support their use (category 2A) for selected patients with resectable, high-risk tumors where curative surgery would result in significant functional impairment or cosmetic morbidity. While definitive phase 3 data comparing neoadjuvant versus adjuvant approaches are pending, these recommendations reflect a paradigm shift toward function-sparing, multimodal management.[35–37]

Adjuvant therapy

The role of adjuvant ICIs following curative-intent surgery for CSCC remains debated. Two pivotal phase 3, randomized, double-blind, placebo-controlled trials (C-POST and KEYNOTE-630) have investigated this approach, yet their outcomes and implications diverge markedly[27 28] (table 2).

In the C-POST trial (NCT03969004), 415 patients with high-risk CSCC were randomized to receive 1 year of cemiplimab or placebo after surgery and adjuvant RT. High-risk features included at least one of the following criteria: extracapsular extension (ECE) with ≥1 node ≥20 mm or ≥3 involved nodes regardless of ECE; in-transit metastases; PNI of named nerves (radiologic or clinical); T4 tumor (bone invasion); or local recurrence with ≥1 adverse feature (≥N2b nodal status, ≥T3 tumor >4 cm, or poorly differentiated histology with recurrence ≥20 mm).[27] Approximately 60% of the study population presented with nodal disease, and about half had ECE. Cemiplimab significantly improved disease-free survival (DFS), with a 24-month DFS of 87.1% vs 64.1% with placebo (HR 0.32, p<0.001).[27] However, no difference in overall survival (OS) was observed at the time of analysis, and the number of events remains low.[27]

In contrast, the KEYNOTE-630 trial (NCT03833167), which randomized 450 patients to receive adjuvant pembrolizumab or placebo in a comparable setting, was terminated early for futility. In fact, the trial failed to demonstrate a significant recurrence-free survival (RFS) benefit (HR 0.76, p=0.07), nor OS, and raised concerns about the risk–benefit profile of pembrolizumab in this context.[28] Importantly, the definition of 'high-risk' disease differed substantially between the two trials. C-POST required extensive nodal disease or major adverse features, whereas KEYNOTE-630 allowed entry based on broader criteria, including microscopic PNI (≥0.1 mm), multifocal small-caliber PNI, large tumor size, satellitosis, or recent recurrence, potentially enrolling a more heterogeneous and overall lower-risk population (table 2).

This distinction is clinically meaningful: PNI of named nerves is associated with aggressive biological behavior, cranial nerve spread, and high early recurrence risk, whereas small-caliber or incidental microscopic PNI carries a much more favorable prognosis. By including patients with PNI of markedly different prognostic weight, KEYNOTE-630 likely incorporated a substantial proportion of individuals already adequately treated by surgery and RT, diluting the potential measurable benefit of adjuvant PD-1 blockade. Moreover, detailed baseline composition regarding the main risk features was not reported for KEYNOTE-630, except for ECE, representing about 40% of both arms. In exploratory analyses, patients with ECE appeared to derive benefit (HR favoring pembrolizumab), whereas in those without ECE the point estimate favored placebo, suggesting that risk 'dilution' and population heterogeneity may have contributed to the neutral primary result.[27 28]

Although an imbalance in deaths was also reported, including non–cancer-related and COVID-19-related fatalities in the pembrolizumab arm, this finding is difficult to interpret and is unlikely to fully explain the absence of an RFS or OS advantage. A more biologically relevant distinction was the interval between completion of RT and randomization: 2–10 weeks in C-POST versus 4–16 weeks in KEYNOTE-630. Since ICIs may require time to exert their full effect, a longer delay could have reduced the likelihood of impacting early micrometastatic relapse. Notably, in KEYNOTE-630, seven patients (3.1%) in the pembrolizumab arm experienced recurrence within ≤3 months of randomization, underscoring the clinical relevance of early events.[27 28]

These conflicting findings highlight a fundamental uncertainty surrounding the biological rationale for adjuvant immunotherapy in CSCC. Unlike melanoma or mucosal head and neck SCC (HNSCC), CSCC lacks validated prognostic biomarkers and consistent definitions of high-risk disease. As a result, many patients included in these trials may have harbored only a modest or heterogeneous risk of recurrence, thereby diluting the ability to detect a meaningful treatment effect. This issue directly reflects the limitations previously discussed in current staging systems—whose inconsistency and poor risk discrimination undermine trial design—and reinforces the need for more accurate and harmonized risk-stratification criteria (see box 1).

Regulatory approvals (FDA/EMA 2025) have established adjuvant cemiplimab as a standard option in resected CSCC; however, its use should be confined to the very high-risk cohort defined in C-POST. Evidence does not support extending adjuvant PD-1 blockade to lower-risk patients, a conclusion reinforced by the negative KEYNOTE-630 trial.

Neoadjuvant therapy

In the neoadjuvant setting, numerous clinical trials have been initiated, although their heterogeneity in design complicates interpretation (table 3). Neoadjuvant studies in CSCC vary widely in eligibility, risk definitions, treatment schedules, and perioperative management. Even within this heterogeneity, early results consistently demonstrate substantial activity of anti-PD-1-based approaches.

The most robust clinical data in support of neoadjuvant ICIs in resectable CSCC derive from two pivotal single-arm phase 2 studies evaluating cemiplimab. In the pilot study conducted by Ferrarotto *et al* (NCT03565783), 20 patients with stage III or IV (M0) CSCC of the head and neck region were treated with two cycles of neoadjuvant cemiplimab prior to curative-intent surgery.[16 17] All patients proceeded to surgery as planned, which is essential when interpreting pathological response rates. Despite the brevity of treatment, 75% of patients exhibited a major pathological response (MPR, defined as ≤10% viable tumor cells), and 55% achieved complete pathological response (pCR).[16 17] Remarkably, clinical benefit appeared durable, with no recurrences reported after a median follow-up of over 30 months, even in the absence of routine postoperative adjuvant therapy.[16 17]

Building on these findings, the larger multicentric trial led by Gross (NCT04154943) enrolled 79 patients with stage II–IV (M0) resectable CSCC, 91% of whom had tumors of the head and neck. Patients received up to four infusions of cemiplimab prior to surgery. Unlike the earlier pilot study by Ferrarotto, in which surgery was largely predefined, this study allowed for response-adapted, less extensive surgery when considered oncologically appropriate, marking an important shift toward de-escalation strategies. Pathologic response rates are again interpretable because all patients undergoing neoadjuvant treatment proceeded to surgical resection unless progression presurgery occurred. The study confirmed a pCR rate of 51% and an MPR rate of 64% as per central pathological review.[14 18] Notably, response rates were largely independent of radiographic assessments, with many pathological responses observed in patients whose imaging only suggested stable or partial disease. Biomarker analyses revealed a trend toward higher response rates in tumors with elevated PD-L1 expression or high tumor mutational burden, although neither parameter emerged as a definitive predictor.[14 18] Treatment was generally well tolerated, although four deaths occurred, three considered unrelated to study therapy. Adjuvant RT was not mandated; in practice, RT was used selectively, a point that further underscores the heterogeneity in postoperative management across trials.[14 18]

The MATISSE trial (NCT04620200) introduced a more pragmatic and potentially transformative approach. In this phase 2, investigator-initiated randomized trial, 50 patients with CSCC requiring extensive or mutilating surgery were allocated to receive two cycles of nivolumab alone or in combination with a single dose of ipilimumab. Surgery was planned for all participants; however, in contrast to other studies, surgery was omitted in 10 patients (20%) who achieved substantial clinical remissions after neoadjuvant therapy. Patients who declined surgery did not receive additional systemic anti-PD-1 therapy.[20 38] Among the patients who underwent resection, MPRs were observed in 40% and 53% of the nivolumab and combination arms, respectively. All nine patients who refused surgery (and, in most cases, RT too) remained disease-free after a median follow-up of 34 months.[20 38] These findings suggest that, in selected patients, short-course immunotherapy alone may be enough, potentially sparing them from disfiguring surgery. However, the omission of both surgery and RT remains highly investigational and requires longer follow-up.

A different strategy was employed in the De-Squamate study (NCT05025813), a phase 2 trial exploring neoadjuvant pembrolizumab for four cycles in 27 patients with resectable stage II–IV (M0) CSCC.[21 26] Treatment response was assessed using a combination of imaging, clinical examination, and mapping biopsies. In patients with complete clinical and metabolic response, both surgery and postoperative RT were omitted. The composite

endpoint of either pCR or clinical complete response was achieved in 63% of participants.[21 26] Importantly, in this trial, omission or de-escalation of RT was protocol-driven and explicitly linked to pathological and clinical response (cCR). None of the patients who achieved such responses experienced recurrence during the median follow-up. These results endorse the feasibility of a de-escalation approach in well-selected patients.[21 26]

In the NEO-CESQ trial (NCT04632433), 23 patients with high-risk stage III–IV (M0) CSCC received two cycles of cemiplimab before surgery, followed by 1 year of adjuvant cemiplimab. In contrast to MATISSE and De-Squamate, surgery was mandatory and RT was not planned, eliminating variation related to local management in responders. A pathological response was observed in 52% of cases (39% pCR; 8% near-pCR).[22]

A further phase 2 trial (NCT04808999) examined pembrolizumab in 30 patients with resectable, locally advanced CSCC defined as AJCC T3 or higher, or T2 with at least two BWH high-risk features. After two cycles of pembrolizumab, followed by curative surgery and planned adjuvant immunotherapy, 57% of patients achieved a pCR. Importantly, RT was safely omitted in over half of those with pathological responses.[19] Although one possible treatment-related death occurred, the safety profile was generally consistent with previous studies. The trial also included exploratory spatial immunophenotyping, which suggested a role for macrophage-PD-L1 interactions as potential mediators of response.[19]

Collectively, these trials highlight not only the promising efficacy of neoadjuvant anti-PD-1-based therapies, but also the profound heterogeneity in trial design, patient selection, response evaluation, and postoperative management (table 4). Handling of RT varied significantly across studies, ranging from obligatory (pilot cemiplimab) to selectively omitted (Gross, De-Squamate, Amatore), to omitted alongside surgery (MATISSE), to entirely excluded from the protocol (NEO-CESQ). The ongoing phase 3 NRG-HN014 trial (NCT06568172), despite incorporating a response-adapted strategy, still mandates surgery and relies on clinicopathologic staging, potentially limiting the exploration of true de-escalation approaches. Definitions of 'high-risk' disease vary substantially, ranging from anatomical and histopathological criteria to AJCC/BWH staging, and no consensus exists regarding the need for surgery or adjuvant therapy in responders.

In this context, the use of event-free survival (EFS), already adopted as a standard endpoint in neoadjuvant melanoma trials,[39] would represent an optimal outcome measure across CSCC studies, as it captures clinically meaningful events (progression presurgery, failure to proceed to surgery, recurrence postsurgery) irrespective of whether patients ultimately undergo surgical resection or not. Despite these differences, a consistent signal of efficacy emerges, with pCR/MPR/cCR rates typically ranging between 50% and 70%. Importantly, pathological and clinical complete responses appear to be strong prognostic markers, echoing findings from melanoma data linking MPR to durable survival benefit.[40 41]

Almost all available trials were single-arm, and variability in inclusion criteria makes it difficult to determine which features truly represent low-risk or high-risk disease, underscoring that risk stratification remains unresolved. Until more definitive survival outcomes and quality-of-life data become available from randomized trials comparing neoadjuvant, upfront surgery, and adjuvant-only strategies, the optimal therapeutic algorithm remains undefined.

Neoadjuvant versus adjuvant therapy

The role of ICIs in early-stage CSCC is evolving, with increasing attention toward neoadjuvant strategies. Compared with the adjuvant setting, where benefit remains uncertain and OS has not improved despite positive data on DFS in one study,[27] neoadjuvant immunotherapy offers several theoretical and clinical advantages. Preoperative administration allows for real-time assessment of tumor response, potentially enabling treatment adaptation or surgical de-escalation in anatomically critical sites. Furthermore, by engaging the immune system in the presence of intact tumor antigen, neoadjuvant ICIs may generate a more robust and durable systemic antitumor response, as shown in many other cancer types.[42]

Multiple neoadjuvant trials in CSCC have demonstrated high pathological response rates, often exceeding 50%, supporting the potential for integration into multimodal management.[14 16–22] In contrast, the adjuvant landscape remains conflicted. While the C-POST trial met its primary endpoint in DFS, it showed no OS benefit.[27] The KEYNOTE-630 trial, meanwhile, was terminated for futility and revealed a higher rate of early mortality in the pembrolizumab arm (7.6% vs 3.1%), raising concerns of overtreatment in a population with curable disease.[28]

Taken together, these data suggest that neoadjuvant immunotherapy may offer a more biologically rational and clinically advantageous approach, particularly when surgical morbidity is a concern or when tumor response could guide the need for further treatment. Future trials should prioritize harmonized endpoints and incorporate biomarker-based selection to better define the patients most likely to benefit.

DISCUSSION AND FUTURE DIRECTIONS

Despite recent progress, substantial methodological and clinical challenges continue to hamper the development of evidence-based strategies in resectable CSCC. The major unresolved issues are summarized in box 1, including the lack of a consistent staging system, the heterogeneity of 'high-risk' definitions across trials, and the absence of consensus on whether surgery or adjuvant therapy are needed in responders. These limitations permeate current trial design. The rationale, design, and implications of ongoing studies are founded on assumptions poorly aligned with the biological and

Table 4 Characteristics of the ongoing neoadjuvant clinical trials for resectable cutaneous squamous cell carcinoma (CSCC)

Study (NCT ID)	Population	Study design	Neoadjuvant intervention	Adjuvant phase	Primary endpoints	Definition of high risk	Mandatory surgery
Winship 4851–19 (NCT04428671)	High-risk, resectable	Phase 1, single arm	Cemiplimab; 4 cycles (12 weeks)	Mandatory; 1 year of treatment, ±RT	Pathological response rate	Nodal disease (ECE or ≥20 mm), in-transit metastases (>2 cm), T4 head/neck tumors, perineural invasion, or recurrent CSCC with advanced nodal/bone involvement or poor differentiation	Yes
MIA NEO-SCC (NCT06288191)	Stage II-IV resectable	Phase 2, single arm	Nivolumab+Relatlimab; 3 cycles (9 weeks)	N/A	pCR	Not specified	Yes
NCT06384820	Stage III/IV perioperative	Phase 2, multiple arms	Cemiplimab±Fianlimab and/or other agents; Up to 3 cycles (9 weeks)	Mandatory; Up to 48 weeks	pCR	Not specified	Yes
ML42362 (NCT04710498)	Resectable	Phase 2, single arm	Atezolizumab; 3 cycles (9 weeks)	N/A	% completion of neoadjuvant therapy and surgery	Not specified	Yes
V940-007 (NCT06295809)	Stage II–IV (M0), resectable	Phase 2/3, three arms	A: V940+Pembrolizumab; B: SOC; C: Pembrolizumab; Up to 4 cycles (12 weeks)	Mandatory in arms A and C; Up to 12 months	EFS	Not specified	No (surgery avoidance possible with complete response)
NCT04975152	Stage III–IV (M0) CSCC, or selected stage II (≥3 cm in cosmetically sensitive sites)	Phase 1, single arm	Cemiplimab; 2 cycles (6 weeks)	Not specified	TRAEs rate	Not specified	Yes
NCT05858229	Resectable	Phase 1/2, single arm	RP1 (oncolytic virus); Up to 8 injections over 16 weeks	N/A	Pathologic response at 16 weeks	Not specified	Yes

Continued

Table 4 Continued

Study (NCT ID)	Population	Study design	Neoadjuvant intervention	Adjuvant phase	Primary endpoints	Definition of high risk	Mandatory surgery
NeoPOWER (NCT04315701)	High-risk localized, locally recurrent, or regionally advanced resectable	Phase 2, single arm	Cemiplimab; 3 cycles (9 weeks)	N/A	pPR	Tumors >2 cm (or >1 cm in high-risk sites), adverse pathology (depth >6 mm, poor differentiation, perineural invasion), or recurrent/regionally advanced CSCC (including ITMs or N+)	Yes
NEOPECS (NCT06418724)	Borderline resectable locally advanced	Phase 2, single arm	Cetuximab+Cemiplimab; Up to 4 cycles (12 weeks)	Not specified	Preliminary activity (clinical downstaging)	Borderline resectable due to prior RT/ recurrent or extensive disease (bone or deep invasion), high surgical morbidity risk, and ineligible for curative RT	Yes
NRG-HN014 C-PRE (NCT06568172)	Resectable stage III–IV (M0) CSCC (including selected immunosuppressed)	Randomized phase 3 (1:1)	Cemiplimab 350 mg Q3W (up to 4 doses) vs upfront surgery (SOC arm); 9–12 weeks	Response-adapted: none if pCR; RT±cemiplimab if <pCR; Cemiplimab 700 mg Q6W×4 (if <pCR) + RT per pathology	EFS	Clinicopathologic staging (stage III–IV; resectable disease)	Yes (in both arms)

This table summarizes key aspects of neoadjuvant clinical trials in CSCC, including study design, population, intervention, duration of treatment phases, and primary endpoints. The inclusion of an adjuvant phase is specified where applicable. The table highlights differences in study designs, the definition of high-risk disease, and the requirement for mandatory surgery across trials.
ECE, extracapsular extension; EFS, event-free survival; N/A, not available; pCR, pathological complete response; Q3W, every 3 weeks; Q6W, every 6 weeks; RT, radiotherapy; SOC, standard of care; TRAE, treatment-related adverse event.

clinical peculiarities of CSCC. Most importantly, they often import rigid frameworks from HNSCC and melanoma, particularly the inclusion of adjuvant therapy irrespective of response, and without adequately accounting for the unique features of CSCC.

A conceptual overview of clinical decision-making in early-stage CSCC is provided in figure 1, which illustrates the heterogeneity of patient presentations, the limitations of current risk-stratification systems, and the emerging role of neoadjuvant immunotherapy within response-adapted pathways.

CSCC is not melanoma nor HNSCC. It predominantly affects elderly, often immunosuppressed and frail individuals, arises in sun-exposed and anatomically complex sites, and carries a highly variable risk of recurrence after R0 resection.[43] Yet, unlike melanoma, CSCC still lacks a robust, universally adopted prognostic framework. Existing staging systems (AJCC, BWH, UICC) offer only modest risk discrimination and often omit key variables such as immunosuppression, tumor growth rate, and high-risk anatomical locations (table 1).[23 29 30 44 45] As a result, even in the presence of adverse features, baseline recurrence risk remains poorly defined—making the rationale for a full year of adjuvant PD-1 blockade inherently uncertain. Moreover, the impressive pCR rates of 39%–57% achieved with neoadjuvant anti-PD-1 therapy in resectable CSCC derive almost exclusively from UV-driven tumors in sun-exposed skin. This efficacy depends on UV-induced high tumor mutational burden (~45 mutations/Mb), generating abundant neoantigens.[46] Non-UV-induced CSCC (Marjolin's ulcer, Recessive Dystrophic Epidermolysis Bullosa, chronic wounds) shows sixfold lower TMB, distinct mutational signatures, and dramatically inferior outcomes: objective response rate (ORR) 22% vs 79%, median time-to-progression of 1.6 vs 51.6 months (HR 5.5, p=0.001).[47] These data argue against extrapolating neoadjuvant trial results to non-UV CSCC and support stratification by etiology in future trial designs.

A striking common feature across most neoadjuvant trials in CSCC is the inclusion of a fixed adjuvant phase, regardless of response to initial therapy. This design choice seems more rooted in the HNSCC and melanoma template than in disease-specific rationale. For instance, some studies included mandatory postoperative anti-PD-1 up to 12 months, even in patients who achieved MPR.[19 22]

This approach has now been seriously challenged. In fact, phase 2 and 3 studies in melanoma have shown that adjuvant immunotherapy can be safely omitted in patients achieving MPR, without compromising long-term outcomes.[40 41 48] These advances offer an important lesson for CSCC. In this population, response-adapted approaches may allow avoiding prolonged systemic therapy, surgical morbidity, and the risk of long-term sequelae or impairment of quality of life. Moreover, CSCC rarely leads to rapid visceral dissemination, and the risk of losing a curative opportunity due to early systemic relapse is significantly lower than in melanoma. This supports a de-escalation strategy in patients achieving deep responses to neoadjuvant therapy.

The recent discontinuation of the V940-007 trial, following the negative results of KEYNOTE-630, clearly indicates that adjuvant pembrolizumab does not confer meaningful benefit in resected CSCC.[28 49] Yet, what makes the termination of V940-007 particularly regrettable is the fact that it represented a bold and innovative therapeutic strategy: the integration of a personalized mRNA-based vaccine targeting patient-specific neoantigens into a perioperative immunotherapy regimen.[49] The study design included three arms: individualized neoantigen therapy plus pembrolizumab administered both in the neoadjuvant and adjuvant setting with standard of care, pembrolizumab monotherapy with standard of care, and standard of care alone. Instead of preserving and interrogating this innovation in a flexible design, the trial was structurally anchored to the dogma of mandatory surgery and adjuvant therapy, leading to its closure once the supposed clinical rationale was weakened. This misalignment between scientific ambition and clinical conservatism represents a lost opportunity for the field and underscores the need to decouple innovative immunotherapeutic approaches from legacy models derived from other tumor types.

Another inherited constraint is the obligatory surgical resection following neoadjuvant therapy, regardless of clinical or radiologic response. Yet, both the MATISSE and De-Squamate studies offer compelling counterpoints: in MATISSE, nine patients declined surgery and RT following good clinical response to just two cycles of immunotherapy and remained recurrence-free with excellent quality of life. De-Squamate adopted a response-adapted algorithm including clinical, metabolic, and biopsy-confirmed complete response to de-escalate not only RT but also surgery in selected cases.[20 21 26 38]

These results not only demonstrate the feasibility of non-surgical strategies in selected patients but also question whether surgery should remain an immutable endpoint in neoadjuvant CSCC trials. In fact, the role of mapping biopsies in patients achieving major clinical response after neoadjuvant immunotherapy remains an area of active debate. Radiological assessment alone may be insufficient, as substantial discordance between imaging and pathological response has been reported.[14 50] Emerging strategies aim to integrate tissue confirmation into response-adapted decision-making: the De-Squamate study prospectively incorporated mapping biopsies alongside FDG-PET to guide surgery omission, reporting no recurrences in patients meeting combined criteria, whereas other trials such as MATISSE relied primarily on metabolic imaging, with a small but non-negligible risk of progression in patients who declined surgery.[26 38]

Pathologic response has emerged as a robust surrogate for survival in CSCC, with MPR (≤10% viable tumor) predicting negligible recurrence rates in neoadjuvant trials.[14 16–18] However, the lack of standardized response criteria, exemplified by divergent definitions of partial response across studies, remains a challenge. Clinically, these prognostic signals are now driving response-adapted strategies aimed at therapeutic

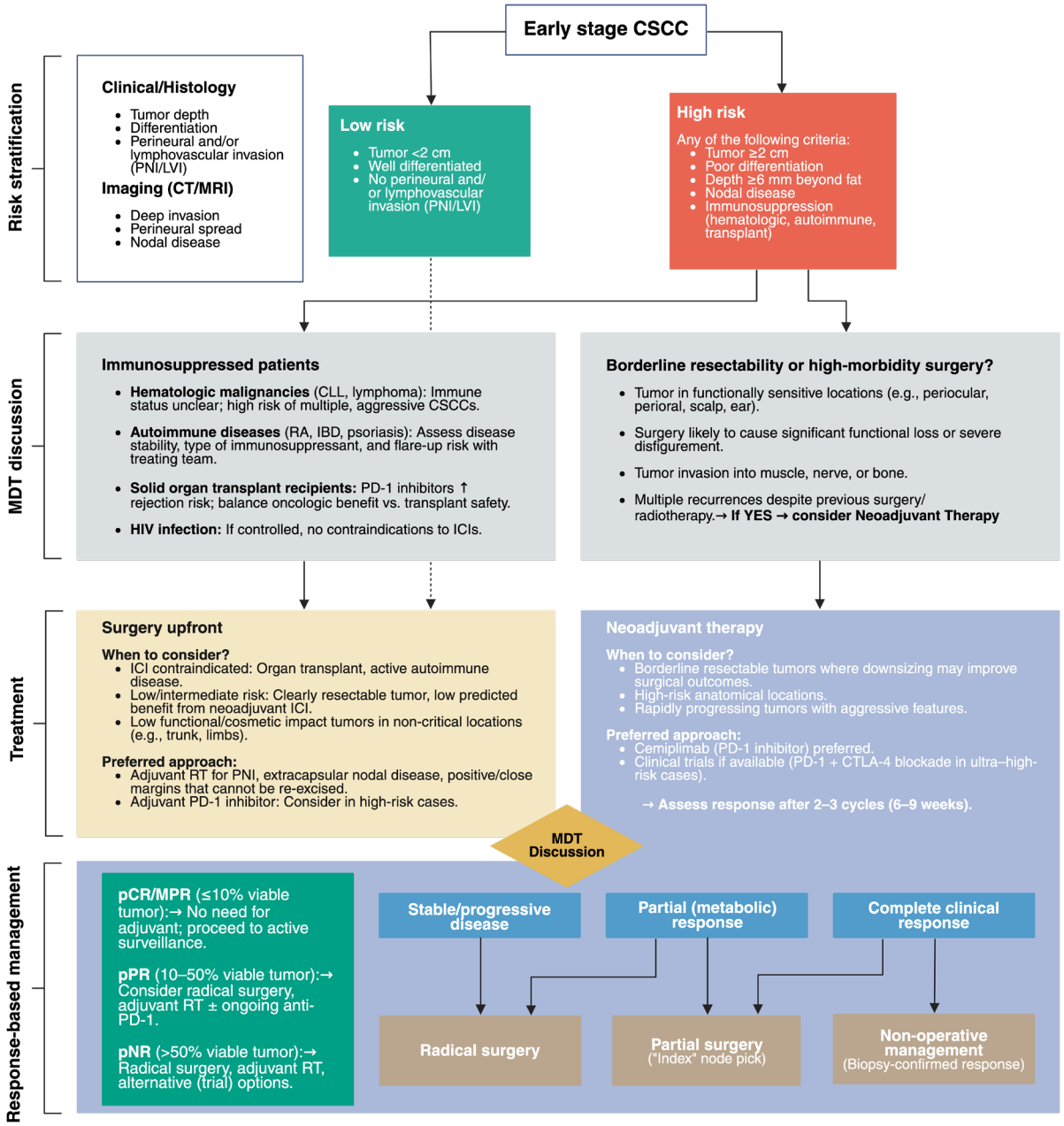

Figure 1 Clinical decision-making algorithm for high-risk early cutaneous squamous cell carcinoma (CSCC). The algorithm outlines risk stratification and treatment pathways based on histopathologic and imaging assessments. Low-risk patients (tumor <2 cm, well-differentiated, no perineural invasion (PNI), defined based on clinical/radiologic findings or histopathologic assessment, or lymphovascular invasion (LVI)) undergo wide local excision with surveillance. High-risk patients (tumor >2 cm, poor differentiation, PNI/LVI, deep invasion, nodal disease, or immunosuppression) require multidisciplinary team (MDT) discussion. Treatment options include surgery upfront (for clearly resectable tumors, immune checkpoint inhibitor (ICI) contraindications, or low predicted benefit from neoadjuvant therapy, with adjuvant radiotherapy (RT) or PD-1 inhibitors in select cases) or neoadjuvant therapy (for borderline resectable tumors, high-risk anatomical locations, or aggressive disease, typically using PD-1 inhibitors). Response assessment should integrate clinical examination, cross-sectional imaging (CT or MRI), and, in selected cases, FDG-PET, while pathological evaluation remains the most informative endpoint when surgery is performed. Major pathological response (MPR) is a promising surrogate endpoint in CSCC but is not yet validated to the same extent as in melanoma. Response-based management stratifies patients into surveillance (pathologic complete response (pCR) or MPR: ≤10% viable tumor), adjuvant therapy (pathologic partial response (pPR): 10%–50%), or radical surgery (pathologic non-response (pNR): >50%), guiding further intervention. Baseline predictive biomarkers (eg, PD-L1 expression or tumor mutational burden) have not demonstrated consistent clinical utility in CSCC. In contrast, early on-treatment imaging biomarkers are emerging as promising tools: in the MATISSE trial, early changes in FDG-PET-derived total lesion glycolysis (TLG) demonstrated high accuracy (up to ~96%) in identifying responders to neoadjuvant immunotherapy, supporting their potential role in response-adapted treatment strategies.

Box 2 Strategic priorities and future directions in early-stage cutaneous squamous cell carcinoma (CSCC)

Develop a harmonized CSCC-specific staging system
- ⇒ Integrate clinical, pathological, anatomical, and immunological variables to improve risk prediction.
- ⇒ Enable consistent eligibility criteria across studies and guide decision-making in routine practice.

Standardize the primary endpoint: Event-free survival (EFS)
- ⇒ EFS captures all clinically relevant events (progression during induction, inability to proceed to surgery, postoperative recurrence).
- ⇒ Unlike disease-free survival, EFS allows comparison across designs where surgery may be omitted.
- ⇒ Validated in melanoma and directly transferable to CSCC neoadjuvant trials.

Implement response-adapted surgical and radiotherapeutic pathways
- ⇒ Allow omission or de-escalation of radical surgery and radiotherapy in patients achieving metabolic, radiologic, or pathological complete response.
- ⇒ Prioritize organ preservation, functional outcomes, and patient quality of life.

Broaden eligibility criteria to reflect real-world CSCC
- ⇒ Include elderly, frail, and immunosuppressed patients, the groups most affected by CSCC but least represented in trials.
- ⇒ Reduce exclusion based on arbitrary definitions of "high-risk."

Prioritize neoadjuvant over adjuvant strategies
- ⇒ Neoadjuvant anti-PD-1 yields high rates of pCR/MPR (50%–70%), enabling de-escalation of local therapy.
- ⇒ Adjuvant immunotherapy lacks proven benefit and risks overtreatment.

Integrate biomarkers and advanced pathology
- ⇒ Include TMB, immune infiltrates, IFNγ signatures, $CD39^+$ Tregs, PET metrics, and spatial immune profiling.
- ⇒ Use biomarkers to personalize neoadjuvant treatment intensity and refine surgery/radiotherapy decisions.

Together, these priorities provide a roadmap for a modern, biology-informed, response-driven approach to early-stage CSCC, better aligned with patient needs and real-world clinical practice.

de-escalation. For instance, the De-Squamate trial introduced a paradigm of 'total de-escalation', omitting both surgery and RT in patients with a confirmed clinical complete response (determined by metabolic imaging and negative mapping biopsies). Conversely, 'partial de-escalation' (omitting adjuvant RT) is increasingly validated for patients achieving deep pathologic responses after resection.[26 38] This shift toward biology-guided management, potentially aided by advanced metabolic imaging,[51] promises to spare selected patients the morbidity of trimodality therapy without compromising oncologic control.

Our proposed algorithm (figure 1) offers a response-adapted approach that reflects both the biological heterogeneity of CSCC and the practical needs of its patient population. At the center of this model lies the concept of stratification based on pathologic response following a brief course of neoadjuvant immunotherapy. Patients achieving a pCR or MPR represent a subset with highly favorable prognosis and may be safely observed or receive only RT, thus sparing them from unnecessary prolonged systemic therapy exposure. Conversely, patients with minor or absent pathologic response are re-evaluated within a multidisciplinary setting, where adjuvant immunotherapy or RT may be considered based on comorbidities, resection margins, and residual tumor burden. The algorithm explicitly allows for treatment modulation, including the possibility of avoiding surgery altogether in cases of confirmed clinical and pCR, an approach supported by recent evidence from De-Squamate and MATISSE.[20 21] Importantly, the model avoids a priori decisions regarding adjuvant treatment duration or modality and instead prioritizes patient-specific parameters such as age, immune status, anatomical site, and functional outcomes. By integrating clinical, metabolic/radiologic, and histopathologic data into a unified decision-making process, the algorithm aims to reconcile therapeutic efficacy with real-world applicability, promoting a pragmatic yet biologically informed treatment paradigm. Such models are more in line with modern oncology, prioritizing precision and personalization over protocol rigidity.

A further limitation of ongoing studies is the highly selective inclusion criteria. Many trials exclude immunosuppressed patients, the elderly, or those with comorbidities (such as hematologic malignancies), populations that represent a significant portion of real-world CSCC cases. This creates a paradox where trials designed to address an unmet need end up excluding those most likely to benefit. In fact, solid OTRs represent a particularly challenging subgroup. While lung, heart, and liver transplants carry a high risk of fatal graft rejection with ICIs, kidney transplant recipients represent a more nuanced population, as graft loss is not invariably fatal due to dialysis. In a 2025 meta-analysis (n=331), rejection rates were highest in kidney (46.3%) compared with heart (40.0%) and liver (26.9%), yet kidney recipients had lower all-cause mortality (HR 0.51) because rejection is survivable with dialysis, whereas non-kidney recipients have higher mortality (HR 1.95) due to limited salvage options.[52 53] In selected kidney transplant recipients, anti-PD-1 therapy showed activity in advanced CSCC (46%–61% ORR) but significant rejection risk (23%–46%).[53 54] This risk can be managed through multidisciplinary evaluation and a regimen of mTOR inhibitors plus steroids.

In addition, data from the DeCOG group have shown that concomitant hematologic malignancies, particularly chronic lymphocytic leukemia, are associated with significantly poorer outcomes to ICIs in CSCC (ORR 26.7%, median PFS 4.0 months), suggesting that underlying immune dysfunction may critically impair treatment efficacy in this population.[55]

Moreover, the reliance on resectable stage III–IV or high-risk stage II disease (often defined variably) with Response Evaluation Criteria in Solid Tumors measurable disease only creates further heterogeneity and impairs cross-study comparisons. A harmonized, inclusive, and risk-adapted eligibility framework is urgently needed.

Future research in early CSCC should shift toward pragmatic, adaptive designs. Rather than rigidly adhering to

fixed treatment durations and inclusion criteria, studies should adopt flexible architectures that incorporate consistent risk stratification tools, encompass elderly and immunosuppressed patients, integrate radiologic and pathologic response for therapeutic decisions, and allow for individualized modulation of surgery and adjuvant therapy. The evaluation of quality of life and functional outcomes should accompany survival endpoints to reflect the clinical reality of CSCC. In parallel, it is imperative that clinical guidelines evolve to reflect the unique characteristics of CSCC, rather than mirroring paradigms established in melanoma or HNSCC. These tumors differ in terms of pathogenesis, patient population, anatomical considerations, and immune microenvironment. Guideline committees should therefore resist the temptation to apply a 'one-size-fits-all' template and instead endorse disease-specific, evidence-informed flexibility that acknowledges both the biological and clinical peculiarities of CSCC. Taken together, these considerations highlight the need for a coherent, biologically informed framework to guide the next generation of CSCC clinical trials. The strategic priorities required to achieve this evolution are summarized in box 2.

CONCLUSIONS

Perioperative immunotherapy represents a promising frontier in early-stage high-risk CSCC. Yet its successful implementation depends on abandoning rigid templates (from different cancer types) and embracing the unique biological, clinical, and demographic context of this disease. Current trials must be redesigned with greater flexibility, guided by the biology of CSCC, the characteristics of its predominantly elderly and comorbid patient population, and the nuances of tumor behavior that are not adequately captured by existing staging systems. Only through a shift toward dynamic, response-adapted, and patient-centered approaches can we ensure that perioperative strategies deliver meaningful benefit without undue burden. CSCC must be approached on its own terms, with its own evidence base and its own standards of care.

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