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Closing in on Anal Cancer: Has the Era of Immune Checkpoint Inhibitors Truly Arrived?

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ABSTRACT

Squamous cell carcinoma of the anus (SCCA) is a rare malignancy, with rising incidence and mortality largely attributed to human papillomavirus (HPV) infection. While chemoradiotherapy remains the standard treatment for locoregional disease, the management of recurrent or metastatic SCCA has long been a challenge due to limited therapeutic options and poor prognosis. Recent advancements, particularly the use of immune checkpoint inhibitors (ICIs), have revolutionized the treatment landscape. It has been demonstrated that combining carboplatin-paclitaxel with immunotherapy improves progression-free survival (PFS) and overall survival (OS) in metastatic SCCA, representing a practice-changing development. HPV-positive tumors, with their distinct immunogenic profile, have shown promise in responding to ICIs, although the risk of increased toxicity remains. Current research continues to explore novel treatment combinations, including ICIs, targeted therapies, and chemoradiotherapy, to enhance treatment outcomes and overcome resistance mechanisms. As ICIs gain a more central role in the treatment of SCCA, ongoing trials and future studies will define the optimal strategies for improving patient outcomes in both early and advanced disease.

Keywords: Squamous cell carcinoma of the anus, immunotherapy, immune checkpoint inhibitors, HPV, metastatic anal cancer

Introduction

Anal cancer is a relatively rare malignancy, representing less than 3% of all gastrointestinal cancers.[1] The majority of cases are classified as squamous cell carcinoma of the anus (SCCA).[1,2] Over the past few decades, both the incidence and mortality of anal cancer have been increasing in several countries, largely attributable to the rising prevalence of human papillomavirus (HPV) infection, which is the primary etiological factor in most SCCA cases.[2,3] The majority of patients with SCCA present with locoregional disease, for which chemoradiotherapy (CRT) remains the standard treatment, offering curative potential in many cases. Five-year overall survival (OS) rates for locoregional SCCA are approximately 70%.[4] However, metastatic or recurrent SCCA poses a significant clinical challenge, as treatment options are limited and the prognosis remains poor.[4]

Prior to the InterAAct phase II trial, first presented in 2018, there were no prospective studies on the first-line treatment of metastatic SCCA, and the available data from retrospective analyses were sparse, leaving few established therapeutic options.[5] Until that point, the combination of fluoropyrimidine and platinum-based agents was considered the first-line therapy of choice.[6,7] The pivotal InterAAct study demonstrated that carboplatin combined with paclitaxel provided superior outcomes compared to the previous standard regimen of cisplatin plus 5-fluorouracil (5-FU), with fewer severe adverse events (AEs). Median OS improved from 12.3 months for cisplatin plus 5-FU to 20 months for carboplatin plus paclitaxel (HR 2.00; p = 0.014).[8] Since this trial, additional systemic therapies have been investigated for SCCA across various lines of treatment.

Immunotherapy, specifically immune checkpoint inhibitors (ICIs), has revolutionized cancer treatment, particularly in malignancies associated with viral infections such as HPV.[9] The success of immunotherapy in other HPV-associated cancers, such as cervical and oropharyngeal carcinomas, [10,11] has spurred interest in its application in SCCA. This review examines the evidence supporting the use of immunotherapy in SCCA, focusing on immune checkpoint blockade and its potential role in various clinical settings.

Pathogenesis of SCCA and the Role of HPV

The pathogenesis of SCCA is closely linked to persistent infection with high-risk HPV strains. The oncogenic HPV strains, particularly HPV-16, drive tumorigenesis through the expression of viral oncoproteins E6 and E7.[12] These proteins inactivate critical tumor suppressor genes such as p53 and retinoblastoma (Rb), leading to uncontrolled cell proliferation, genomic instability, and tumor development.[13,14] HPV-positive tumors, including SCCA, often exhibit a distinct immunogenic profile compared to HPV-negative tumors, characterized by increased immune cell infiltration into the tumor microenvironment (TME).[15]

The presence of viral antigens such as E6 and E7 proteins allows the immune system to recognize and potentially target these cancer cells. However, despite this, HPV-associated cancers, including SCCA, have developed immune evasion mechanisms.[16] Tumor cells exploit immune checkpoint pathways, such as the programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis, to escape immune surveillance.[16-18] This provides the rationale for targeting these pathways using ICIs, which aim to re-engage the immune system in recognizing and destroying tumor cells.

Retrospective analyses indicate that PD-L1 expression is found in 40.5% to 61% of SCCA cases.[17,18] PD-L1-positive tumors are significantly associated with improved disease-free survival (DFS) and OS (p = 0.006 and p = 0.002, respectively), as well as an increased likelihood of achieving a complete response (odds ratio = 8.50, 95% CI, 2.44–53.62; p = 0.004) following definitive chemoradiotherapy compared to PD-L1-negative tumors.[19] Thus, PD-L1 expression status may serve as an independent prognostic marker for survival, highlighting its importance for treatment stratification with ICIs in conjunction with chemotherapy.

While there is no conclusive link between HPV infection and PD-L1 expression,[18] a prospective study involving 150 patients with SCCA found that those with elevated PD-1 and tumor-infiltrating lymphocytes (TIL) showed significantly better DFS, OS, and improved local control after CRT.[20] Additionally, in a study of two cohorts of anal cancer patients, HPV-positive SCCA tumors with high TIL levels demonstrated significantly higher relapse-free survival rates compared to those with low or absent TILs (92% vs. 63%).[21] These findings highlight the robust immune cell infiltration in HPV-positive SCCA, but further research is needed to fully understand its impact on survival and personalized treatment strategies.

Definitive treatment

Several ICIs are being evaluated in prospective trials, both in conjunction with CRT and as adjuvant therapy for high-risk recurrent tumors,[22-28] as shown in Table 1.

Table 1: Ongoing studies using immune checkpoint inhibitors with definitive treatment.

Study NCT Identifier	Phase	Population	Treatment Arms
CORINTH[22] NCT04046133	Ib/II	Stage IIIA or IIIB (T3-4Nx M0)	Pembrolizumab + CRT
INTERACT-ION[23] NCT04719988	II	TxN1 or T4N0	Ezabenlimab + mDCF + RT
EA2165[24] NCT03233711	III	High Risk Stage II-IIIB	5FU/MMC+RT or Cap/MMC+RT or 5FU/Cisplatin+RT Randomization Arm A: Nivolumab 480 mg IV every 4 weeks Arm B: Observation

Study NCT Identifier	Phase	Population	Treatment Arms
AMC110[25] NCT04929028	II	T3-T4N0M0 or T2-4N1M0	Low-risk stratum: De-intensified CRT (20 or 23 fractions) High-risk stratum: Nivolumab every 4 weeks x 6 cycles after CRT
RADIANCE[26] NCT04230759	II	Stage IIB-IIIC	5FU/MMC+RT vs 5FU/MMC/Durvalumab+RT
NCT05060471[27]	II	Stage I-III	Neoadjuvant toripalimab, Docetaxel and Cisplatin followed by Toripalimab + RT
TIRANUS[28] NCT05661188	II	Stage I-IIIB, except Stage I anal margin	Tiragolumab + Atezolizumab + CRT followed by maintenance of Tiragolumab + Atezolizumab x 6 cycles

CRT: chemoradiotherapy; mDCF: modified docetaxel, cisplatin, 5-fluorouracil; RT: radiotherapy; 5FU: 5-fluorouracil; MMC: mitomycin; Cap: capecitabine; NCT: Available at: https://clinicaltrials.gov/ Accessed September 26, 2024

As mentioned earlier, HPV-positive SCCA exhibits exuberant immune cell infiltration,[17-19] and anti-PD-1/PD-L1 therapies may act synergistically when combined with radiation therapy in managing non-advanced disease. The results of these studies are eagerly anticipated, with high expectations for success.

The inclusion of ICIs in the definitive treatment of CRT is being explored mainly in the context of higher-risk disease, T3 or T4 and/or N+,[22-25] where better outcomes are needed to minimize disease recurrences. On the other hand, for lower-risk tumors, treatment de-escalation with fewer radiation fractions is being tested to determine whether, in this scenario, patients could be spared toxicities from lower radiation doses without compromising the efficacy of definitive treatment.[25]

Palliative treatment

The landscape of first-line treatment for recurrent or metastatic SCCA has shifted considerably with the presentation of the POD1UM-303/InterAACT 2 trial at ESMO 2024.[29] This phase III trial randomized 308 patients to receive first-line therapy with carboplatin and paclitaxel for six cycles, combined with either retifanlimab or placebo for 12 months. Among the participants, PD-L1 expression was positive (≥1) in 90% of cases, and fewer than 4% were HIV-positive.[29] The trial achieved its primary endpoint of progression-free survival (PFS), with the immunotherapy arm showing a median PFS of 9.3 months compared to 7.4 months in the control arm (HR 0.63; 95% CI 0.47–0.84; p = 0.0006). An interim analysis of OS indicated a median OS of 29.2 months in the combination arm versus 23 months in the control arm (HR 0.70; 95% CI 0.49–1.01; p = 0.0273), although 44.8% of patients in the control group crossed over to the experimental treatment.[29] An OS analysis adjusted for crossover demonstrated an absolute gain of 10.1 months in the immunotherapy arm (29.2 vs. 19.1 months; HR 0.63; 95% CI 0.44–0.90; p = 0.0055). In addition to improved survival outcomes, the immunotherapy group exhibited a higher overall response rate (ORR) (55.8% vs. 44.2%; p = 0.0129). However, increased toxicity was observed in the experimental arm, with grade ≥3 treatment-emergent adverse events (TEAEs) occurring in 83.1% of patients, compared to 75% in the control arm.[29] This phase III trial is the first to demonstrate a benefit from the addition of immunotherapy to first-line systemic treatment for SCCA and is considered practice-changing.

Previously, the randomized phase II SCARCE C17-02 PRODIGE 60 trial evaluated the combination of modified DCF (mDCF) and atezolizumab as first-line treatment in 97 patients but did not achieve its primary endpoint.[30] The 12-month PFS rates were comparable between the two arms (45% in the atezolizumab arm vs. 43% in the control arm). Nevertheless, in patients with PD-L1 expression and a combined positive score (CPS) ≥5, the atezolizumab arm demonstrated a 30% higher 12-month PFS (interaction p = 0.051).[30]

In the second-line setting, single-agent immunotherapy has shown efficacy in managing refractory metastatic or advanced SCCA, as supported by phase II studies (Table 2).[31-27] Although response rates and PFS were modest, the favorable safety profile, with few patients experiencing significant adverse events,[31-34] has led to further investigations combining immunotherapy with chemotherapy. Current NCCN Guidelines® recommend ICIs, including nivolumab and pembrolizumab, as second-line treatment options for metastatic SCCA, although these agents have not yet received FDA approval for this indication.[35]

Table 2. Single agent's immunotherapy results from phase II studies

	drug	N	ORR	PFS	OS	AE G ≥3
NCI 9673[31]	nivolumab	37	24%	4.1 m	11.5 m	13.5%
KEYNOTE-158[32]	pembrolizumab	112	11%	2 m	11.9 m	18%
POD1UM-202[33]	retifanlimab	94	13.8%	2.3 m	10.1 m	6.4%
CARACAS[34]	avelumab	60	10%	2 m	13.9 m	0%

N: number; ORR: objective response rate; PFS: progression-free survival; OS: overall survival; AE: adverse events; G: grade

Despite some retrospective analyses suggesting a potential benefit from anti-EGFR antibodies in recurrent SCCA,[36,37] the prospective phase II CARACAS study indicated that combining anti-EGFR therapy with avelumab does not significantly improve median OS (13.9 months vs. 7.8 months).[34] However, it may offer an improvement in median PFS (2 months vs. 3.9 months) and the primary endpoint of ORR (10% vs. 17%). This combination was associated with a higher incidence of grade ≥3 adverse events (AEs) (33.3% vs. 13.3%) compared to avelumab monotherapy.[34] While the outcomes of the avelumab monotherapy arm are consistent with other single-agent immunotherapy regimens included in current guidelines,[31-35] the potential of anti-EGFR therapy, either alone or in combination, to substantially improve outcomes for patients with SCCA remains unclear.

In an effort to enhance PD-L1 checkpoint inhibition by counteracting immune evasion and suppression within the tumor microenvironment driven by VEGF signaling, the combination of VEGF blockade (via bevacizumab) with atezolizumab was investigated in patients with refractory metastatic SCCA.[38] This small, single-arm phase II study reported a 10% ORR (2 of 20 patients) and a disease stabilization rate of 55%. The median PFS and OS were 4 months (95% CI, 2.6–NA) and 11.6 months (95% CI, 9.5–20), respectively. However, 35% of patients experienced grade ≥3 AEs, including one grade 5 treatment-related AE (bowel perforation). While this combination shows promise, safety concerns warrant further investigation.[38]

Similarly, the combination of ipilimumab and nivolumab did not demonstrate significant improvements in efficacy or survival outcomes compared to single-agent immune checkpoint inhibitors in the NCI ETCTN (NCI9673) trial.[39] The ORR, median PFS, and median OS were 17.4% vs. 21.5% (p = 0.89), 2.9 months vs. 3.7 months (HR 0.80, 95% CI 0.51–1.24; p = 0.16), and 15.4 months vs. 20 months (HR 0.86, 95% CI 0.51–1.47; p = 0.59), respectively, for nivolumab alone versus the nivolumab-ipilimumab combination.[39]

The role of ICIs in the treatment of advanced SCCA continues to be explored through various studies evaluating novel agents, combinations with vaccines, integration with chemotherapy or targeted therapies, and alternative dosing strategies,[40-49] as detailed in Table 3.

Table 3: Ongoing studies using immune checkpoint inhibitors including anal cancer advanced disease.

Study NCT Identifier	Phase	Treatment Arms	Primary endpoint	Status
EA2176[40] NCT04444921	III	Arm A: CBDCA + Paclitaxel Arm B: CBDCA + Paclitaxel + Nivolumab	PFS	Active, not recruiting
SPARTANA[41] NCT04894370	III	Phase 1: Radiotherapy (8 Gy on target lesions) Phase 2: mDCF + Spartalizumab Phase 3: Multimodal treatment of residual disease Phase 4: Maintenance treatment with Spartalizumab	1-year PFS rate	Active, recruiting
NCT05544929[42]	I	Arm 1: KFA115 monotherapy Arm 2: KFA115 run-in (1 cycle) + pembrolizumab Arm 3: KFA115 + pembrolizumab	dose AE	Active, recruiting
NCT04287868[43]	I/II	Arm 1: PDS0101 + NHS-IL12 + M7824	BOR	Active, not recruiting
VolATIL[44] NCT03946358	II	Atezolizumab + UCPVax	ORR	Active, not recruiting
NCT05941507[45]	I/II	Arm 1: LCB84 monotherapy Arm 2: LCB84 + anti-PD-1	safety dose ORR	Active, recruiting
NCT04708470[46]	I/II	Arm 1: dose escalation/de-escalation of entinostat + dose escalation of PDS01ADC + bintrafusp alfa Arm 2: RP2D of entinostat + PDS01ADC + bintrafusp alfa Arm 3: Entinostat + PDS01ADC	ORR RP2D	Active, recruiting
PRESERVE-009[47] NCT05858736		AI-061	dose RP2D AE	Active, recruiting
KEYNOTE-E28[48] NCT04429542	I	Arm 1: BCA101 monotherapy Arm 2: BCA101 + pembrolizumab	safety AE dose	Active, recruiting
KEYNOTE-158[49] NCT02628067	II	Arm 1: Pembrolizumab 200 mg every 3 weeks Arm 3: Pembrolizumab 400 mg every 6 weeks	ORR	Active, recruiting

CBDCA: carboplatin; PFS: progression-free survival; mDCF: modified docetaxel, cisplatin, 5-fluorouracil; AE: adverse events; BOR: best overall response; UCPVax: universal cancer peptide–based vaccine; ORR: objective response rate; PD: programmed death; RP2D: recommended phase II dose; ADC: antibody-drug conjugate. NCT: Available at: https://clinicaltrials.gov/ Accessed October 23, 2024

Since advanced SCCA has limited options for systemic treatment, the use of maintenance therapy with ICIs, as proposed by the SPARTANA study,[41] seems quite logical and addresses a clear need for patients with advanced disease. If the promising data from this strategy are confirmed, we could offer an extension of PFS and OS with a therapy of low toxicity potential, which would allow for quality of life and maintenance of the patient's performance status for a subsequent line of treatment. Eventually, this strategy could enable re-exposure to induction chemotherapy, depending on the patient's tolerance and the time since the initial treatment, similar to what has been explored in other cancers.[50]

Conclusion:

The treatment of SCCA has significantly progressed, especially with the introduction of ICIs. While chemoradiotherapy remains the standard for locoregional disease, advancements in systemic therapies, have established carboplatin-paclitaxel and immunotherapy combinations as effective first-line options for metastatic SCCA, improving progression-free survival and overall survival.

ICIs, particularly in HPV-associated SCCA, have shown promise, though toxicity and optimal treatment strategies remain challenges. Ongoing trials exploring novel combinations of ICIs, targeted therapies, and chemotherapy aim to further improve outcomes. Future research should focus on refining patient selection, minimizing adverse effects, and overcoming resistance mechanisms. ICIs hold the potential to reshape SCCA treatment, offering new hope for better outcomes.

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