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Lower Gastrointestinal Cancers (AB Benson, Section Editor

The Role of Immunotherapy in the Treatment of Anal Cancer and Future Strategies

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Opinion statement

Despite being markedly sensitive to chemoradiotherapy, patients with locally advanced (T3-4 and/or node-positive) squamous cell carcinoma of the anal canal (SCCA) still present high rates of disease recurrence, which is characterized by meaningful morbidity and mortality. Abdominoperineal resection as salvage surgery may be considered for patients with local recurrence, but with an important negative impact in the quality of life. Systemic therapy of advanced SCCA is an unmet clinical need. Palliative chemotherapy for the management of unresectable or metastatic disease yields approximately 60% of objective response rate; however, it still portends a grim prognosis. Based on the recently published InterAACT trial, carboplatin plus paclitaxel has become the standard of care of advanced disease; modified DCF (docetaxel, cisplatin, and 5-fluorouracil) may also be considered for fit patients amenable to intensive therapy. There are no FDA-approved therapies for the treatment of chemorefractory patients. Nevertheless, both nivolumab and pembrolizumab may be considered for these patients with promising results, regardless of PD-L1 expression or other predictive biomarkers. It is estimated that approximately 1 out of 5 patients with SCCA will derive large benefit from PD-1 inhibitors, which may produce considerable durations of response. Ongoing clinical trials exploring the combination of chemotherapy plus immune checkpoint inhibitors in the first-line therapy, combination of anti-PD-1/PD-L1 plus anti-CTLA-4, and emerging immunotherapeutic

approaches, such as adoptive T cell therapies, are eagerly awaited and may bring practice-changing results in the next few years for the treatment of this challenging disease.

Introduction

Squamous cell carcinoma of the anal canal (SCCA) is an orphan disease with more than 8,500 new cases yearly in the USA, but with increasing incidence rates in the past few years [1]. It is etiologically linked to the human papillomavirus (HPV) infection, with higher incidence and prevalence rates in immunocompromised patients, mainly in those infected with HIV.

The standard of care of localized (T1-2N0) and locally advanced disease (T3-4 and/or N+) has been chemoradiotherapy (CRT) for the past five decades [2–8]. The combination of 5-fluorouracil (5-FU) plus mitomycin-C or cisplatin with 50–54 Gy yields high rates of complete response, with approximately 90% of the patients showing no evidence of disease 26 weeks after the completion of the combined modality therapy [3–5]. However, 20% to 44% of the patients will present recurrence in 5-year follow-up, mainly those with T3-4 and/or node-positive disease, and approximately 20% of the patients will succumb to the disease. Disease recurrence is characterized by high morbidity and mortality. Patients with local recurrence amenable to surgery may be candidates to salvage surgery, such as abdominoperineal resection or pelvic exenteration, which present a meaningful negative impact on the quality of life. Those patients with unresectable or systemic recurrence portend a grim prognosis and should be treated with systemic chemotherapy.

The standard of care in advanced disease has recently been established by the completion of the first randomized clinical trial (RCT) in advanced SCCA. The phase II study InterAACT demonstrated the superiority of the combination of carboplatin plus paclitaxel over the regimen composed of 5-FU plus cisplatin in the first-line therapy of unresectable or metastatic SCCA [9••]. But there is no standard treatment for chemorefractory patients. Based on the revolutionary impact of immunotherapy on cancer therapy in the past decade, immunotherapeutic approaches, mainly immune checkpoint inhibitors (ICIs), have been intensively investigated in the management of SCCA, with promising findings.

In this review, we intend to present the current role of immunotherapy in the systemic therapy of SCCA, the ongoing clinical trials evaluating immunotherapeutic approaches, and the emerging strategies being explored in the therapeutic management of this challenging disease.

The standard of care of SCCA

CRT has been the cornerstone of the treatment of non-metastatic SCCA for five decades. The combination of 5-FU (1,000mg/m^2 on days 1–4 and 29–32) plus mitomycin-C (10mg/m^2 on days 1 and 29) with 50–54Gy of radiation therapy (RT) has been evaluated over the last few decades by pivotal RCTs and has remained the standard of care of non-metastatic disease. After improvements in radiation techniques, with intensity-modulated radiation therapy (IMRT) as the current method of choice, and with increased radiation doses and small variances in mitomycin-C doses, Nigro regimen yields 90% of complete response rate at 6 months, 3-year progression-free survival (PFS) of 73%, 5-year overall survival (OS) of 78%, 5-year colostomy-free survival (CFS) of 74%, and grade ≥3 toxicity of 71% [4–6, 8]. T1N0 tumors with well- or moderately differentiated histology may be considered to excision alone, since there is adequate margins and sphincter preservation [10, 11]. NCCN guidelines suggest that

local excision upfront should be reserved to superficially invasive anal cancers, defined as completely excised lesion with less than 4mm of basement membrane invasion and a maximal horizontal spread of less than 8mm [10].

Based on two RCTs comparing the two chemotherapeutic drugs, cisplatin is an alternative to mitomycin-C in combination with 5-FU. The Intergroup Randomized Trial RTOG 98-11 compared conventional CRT with 5-FU plus mitomycin-C vs. induction 5-FU plus cisplatin chemotherapy followed by CRT with 5-FU plus cisplatin [6, 8]. A total of 682 patients with non-metastatic disease were evaluated, and those patients who received mitomycin-C-based treatment had a significant improvement in 5-year DFS (68% vs. 58%, p=0.006), 5-year CFS (72% vs. 65%, p=0.05), and OS (78% vs. 71%, p=0.026). Although local-regional failure was lower (20% vs. 26%), it did not reach statistical significance. There was no difference in grade 3+ long-term toxicity (13% vs. 11%). The delay in the initiation of RT in the induction chemotherapy arm could be the reason for the inferior outcomes in the cisplatin arm. The UKCCR ACT II trial is the largest RCT ever completed in SCCA and compared cisplatin vs. mitomycin-C-based CRT (50.4 Gy), with a secondary randomization to maintenance 5-FU/cisplatin vs. observation in 940 patients [4, 5]. Compared with mitomycin-C-based CRT, patients who received cisplatin-based CRT had no significant difference in the CR rate at 6 months (90% vs. 91%) and grade 3+ toxicity (72% vs. 71%), as well as there was no difference between maintenance (72% vs. 73%) and no maintenance chemotherapy arms (74% vs. 73%) in 3-year PFS. In summary, the combination of 5-FU plus mitomycin-C remains the standard of care, but given the mitomycin-C-related myelotoxicity, cisplatin is an option for immunocompromised or selected elderly patients.

Based on single-arm phase II trials 12–14], capecitabine may be an alternative to infusional 5-FU, and phase II clinical trial suggested that oxaliplatin may be associated to capecitabine in combined modality therapy, with the advantage to not present the cisplatin-related renal toxicity and the mitomycin-related myelotoxicity, but with concerning rates of grade ≥ 3 diarrhea [15]. Cetuximab [16–21], panitumumab [22], and triplet-regimens [23, 24] have also been evaluated concurrently with RT, but they have showed limiting toxicity rates.

The first completed RCT in advanced SCCA has been recently published. InterAACT was an international multicenter randomized phase II trial which compared the efficacy and safety of carboplatin (AUC 5, day 1) plus paclitaxel (80 mg/m^2, days 1, 8, and 15) every 28 days, vs. cisplatin (60 mg/m^2, day 1) plus 5-FU (1,000 mg/m^2, days 1–4) every 21 days, for 24 weeks, in the first-line systemic therapy of unresectable or metastatic SCCA (Fig. 1)[9••]. The primary endpoint was objective response rate (ORR). From a total of 91 patients, 5 were HIV positive, and more than 70% had ≥ 2 metastatic sites. ORR was similar between the two groups: 59% vs. 57%, respectively. However, the taxane-based regimen demonstrated superior median PFS (8.1 months vs. 5.7 months, p=0.564) and OS (20.0 months vs. 12.3 months, HR: 2.00, 95% CI 1.15–3.47, p=0.014). Based on the InterAACT data, carboplatin plus paclitaxel has become the recommended regimen in the first-line systemic therapy of patients with advanced SCCA and the backbone for future RCTs, including combination with immunotherapeutic approaches.

Relevant data has been provided by the Epitopes-HPV01 and -HPV02 single-arm phase II trials, which evaluated the efficacy and safety of the triplet regimen

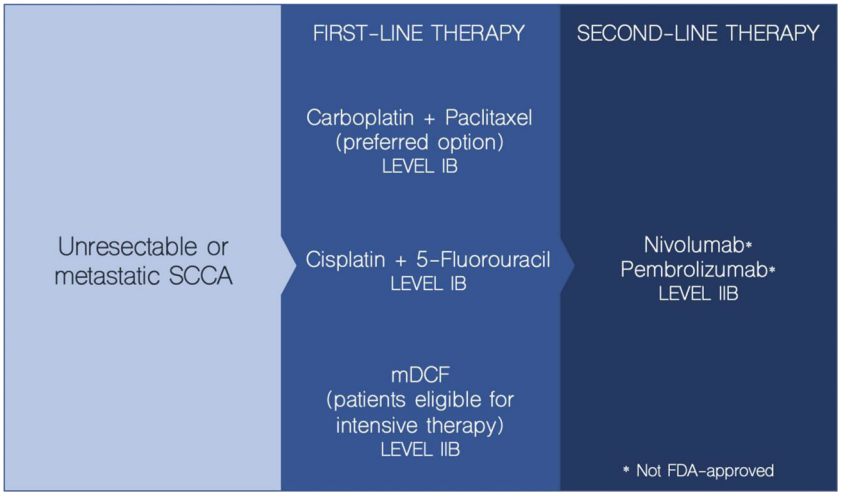

Figure 1. Systemic therapy of unresectable or metastatic SCCA.

DCF (docetaxel, cisplatin, and 5-FU) and modified DCF as the first-line systemic therapy of advanced SCCA. A pooled analysis of 115 patients has been recently published and showed median PFS of 12.2 months, median OS of 39.2 months, and ORR of 87.7%, with 40.3% of complete response. The concerning DCF-related toxicity rates (83% of grade ≥ 3 adverse events) prompted the authors to adjust the regimen, which presented a safer toxicity profile, with 53% of grade ≥ 3 adverse events. Five-year PFS and OS rates were 24.5% and 44.4%, respectively. Despite not being derived from RCTs, modified DCF regimen may be considered for those fit patients with advanced SCCA, given the remarkable efficacy demonstrated by the Epitopes-HPV01 and -HPV02 phase II trials.

Patients infected with HIV have a higher risk of developing SCCA. However, as HIV-positive patients are usually excluded from the clinical trials, the best therapeutic management of SCCA patients co-infected with HIV is uncertain. Retrospective studies show conflicting data about efficacy and safety of CRT and palliative chemotherapy in co-infected patients. NCCN guidelines do not recommend modifications on therapeutic strategy based solely on HIV status [10]. Nevertheless, dose reductions of chemotherapeutic drugs and avoidance of mitomycin-C-related myelotoxicity may be considered in those patients with CD4 count < 200μL or clinical evidence of HIV-related diseases.

Molecular characterization of SCCA

The characterization of the molecular landscape of SCCA is essential for the identification of the molecular abnormalities, prognostic and predictive biomarkers, and, thereby, the conception of clinical trials addressing novel therapies and genome-guided personalized therapy. The description of the molecular characteristics of the tumor microenvironment, PD-L1 expression rates, tumor mutational burden, actionable mutations, and microsatellite instability (MSI) status might help predict the applicability of immunotherapy and targeted therapies in the disease.

Molecular and genomic abnormalities common to other HPV-related malignancies have been described in SCCA. Comprehensive genomic profiling studies have consistently demonstrated that PIK3CA gene mutation is the most frequent genetic abnormality in SCCA [25•, 26–28]. Activating mutations and/or gene amplification of PIK3CA may be found in 32% to 88% of SCCA [25•, 26, 27]. Genes important to histone modification, such as MLL3 and MLL2, as well as to DNA damage repair (p53, ATM, HUWE1, BRCA 1, BRCA 2), chromatin remodeling (EP300, SMARCB1, SMARCA4), and activation of Wnt/β-catenin signaling (FAM123B) were also found frequently mutated [25•]. Importantly, clinically relevant genomic alterations, such as KRAS, NRAS, BRAF, EGFR, and HER2, are rarely found in SCCA.

Similarly to other HPV-related malignancies, such as cervical cancer and HPV-positive head and neck cancer, these studies also suggest that SCCA has a low tumor mutation burden (TMB), with a mean number of 2.5–3.5 somatic mutations/Mb, as well as low rates of high-frequency MSI (MSI-H) [26•]. It seems that TMB is low even in the uncommon HPV-negative SCCA, which is associated with a higher probability of p53 mutation [26•].

The role of immunotherapy in SCCA

Completed clinical trials

NCI9673 was the first phase II clinical trial evaluating the role of immunotherapy in SCCA (Table 1)[9••]. Nivolumab, an anti-PD-1 monoclonal antibody, was evaluated in a total of 37 patients with at least one previous line of systemic therapy for surgically unresectable or metastatic disease, regardless of PD-L1 expression. The primary endpoint was ORR, which occurred in nine patients (24%), of which two reached complete response. From the two HIV-positive patients enrolled in the study, one presented partial response. Among the responders, the median duration of response was 5.8 months, and the median reduction of target lesions was 70%. Seventeen patients (47%) had stable disease, totalizing 72% of disease control rate. In a median follow-up of 10.1

Table 1. Completed clinical trials evaluating immune checkpoint inhibitors in SCCA

Author	*n*	Drugs	ORR (%)	CBR (%)	PFS (m)	OS (m)	1-year OS (%)
Monotherapy							
Morris et al.[32]	37	Nivolumab	24	72	4.1	11.5	48
Ott et al.[33]	32	Pembrolizumab	17	58	3.0	9.3	48
Marabelle et al.[34]	112	Pembrolizumab	12	26	2.0	12.0	49
Rao et al.[35]	94	Retifanlimab	14	49	2.3	10.1	NR
Combination							
Morris et al.[37]	20	Atezolizumab + Bev	10	69	4.1	11.6	40
Lonardi et al.[38]	30	Avelumab + Cmab	17	57	3.9	NR	NR
	30	Avelumab	10	50	2.0	NR	NR

Abbreviations: *ORR*, overall response rate; *CBR*, clinical benefit rate; *PFS*, progression-free survival; *OS*, overall survival; *Bev*, bevacizumab; *Cmab*, cetuximab; *NR*, not reported

months, median PFS was 4.1 months and OS was 11.5 months, with an estimated 1-year OS of 48%. Anemia (*n*=2), fatigue (*n*=1), rash (*n*=1), and hypothyroidism (*n*=1) were the grade 3 adverse events (AEs). No serious adverse events were reported. Correlative studies found that responders had higher baseline percentages of T cells expressing CD8 and granzyme B; higher concentrations of PD-1 in immune cells in the tumor microenvironment; higher PD-L1 expression on tumor cells and CD45+ leucocytes; higher PD-1, LAG-3, and TIM-3 on CD8+ T cells; and higher dual expression of PD-1 and LAG-3, and PD-1 and TIM-3 on CD8+ T cells.

The efficacy of pembrolizumab, another anti-PD-1 monoclonal antibody, in advanced SCCA was evaluated in the basket trial KEYNOTE-028, a multicenter phase Ib study, which contained 20 cohorts of patients with PD-L1-positive advanced solid tumors. In the SCCA cohort, eligible patients had previously treated unresectable or metastatic disease [29••]. Primary endpoints were safety and ORR. Of 43 patients screened for PD-L1 expression, 32 (74%) had PD-L1-positive tumors. Four patients (17%) reached ORR, with 58% of disease control rate. Two of the four responses were ongoing at the time of the analysis and were sustained for longer than 9 months. Median PFS was 3.0 months and OS was 9.3 months, with a 1-year OS of 47.6%. There were four grade 3 treatment-related AEs (TRAEs), including increased blood thyroid-stimulating hormone (TSH) level and general physical health deterioration (*n*=1 each), and colitis and diarrhea in the same patient. No grade 4 or higher TRAEs were seen.

Pembrolizumab was also evaluated in another multicohort study KEYNOTE-158, in which 112 patients with previously treated unresectable or metastatic SCCA were enrolled, irrespective of PD-L1 expression [30]. The primary endpoint was ORR by an independent central review. Five patients reached complete response and eight had partial response (ORR 12%). PD-L1 combined positive score (CPS) ≥1 was found in seventy-five patients (67%), who presented 15% of ORR, while patients with PD-L1 CPS < 1 had 7%. In the overall population, median PFS was 2.0 months and OS was 12.0 months. Five grade ≥3 immune-related AEs were reported: pneumonitis, colitis, skin reaction, adrenal insufficiency, nephritis (one each).

POD1UM-202 was a single-arm phase II trial which evaluated the efficacy and safety of retifanlimab, a humanized IgG4 anti-PD-1 monoclonal antibody, in 94 pts with previously treated advanced SCCA, of which nine were HIV positive [31]. Similarly to the other phase II trials with anti-PD-1 inhibitors in SCCA, the primary endpoint was ORR, but assessed by an independent central review. One complete response and twelve partial responses were reported (ORR 14%), associated with 35% of stable disease. Responses were observed regardless of PD-L1 expression, liver metastases, or HIV status. In a median follow-up of 7 months, median PFS and OS were 2.3 and 10.1 months, respectively. Responses were associated with marked prolongation of PFS and OS. Safety profile was as expected for a PD-1 inhibitor, even in the HIV-positive patients, with 2% of treatment discontinuation due to immune-related AEs.

AMC 095 was a phase I trial which evaluated the safety of nivolumab in a population of patients with HIV-associated solid tumors [32]. Patients received

nivolumab 3 mg/kg each 2 weeks in two dose de-escalation cohorts stratified by CD4 count (stratum 1: CD4 count >200μL and stratum 2: CD4 count 100–200/μL). An expansion cohort of 24 patients with CD4 count >200μL was then enrolled. A total of 37 patients were included, of which 5 had SCCA. There were no patients with dose-limiting toxicities. TRAEs were experienced by 14 patients (38%). The most common TRAEs were fatigue (*n*=5) and maculopapular rash (*n*=4). ORR by the modified WHO criteria was 24%, including 1 patient with SCCA. There were no significant changes detected in HIV viral load during the study. Therefore, nivolumab was safe and effective in a population of patients with HIV-associated solid tumors, including SCCA, with CD4 count > 100μL and undetectable viral load.

Clinical trials exploring the combination of ICIs with antiangiogenics and anti-EGFR monoclonal antibodies have been recently presented. The combination of atezolizumab 1200mg, an anti-PD-L1 monoclonal antibody, plus bevacizumab 7,5mg/kg, each 3 weeks, was evaluated in a single-arm phase II study with 20 patients with unresectable or metastatic SCCA [33]. Nineteen patients were evaluable for response. ORR, the primary endpoint, was seen in two patients (10%), with stable disease in 11 patients (58%). With a median follow-up of 9.6 months, median PFS and OS were 4.1 months and 11.6 months, respectively. Grade ≥3 AEs were observed in 7 patients (35%), with one grade 5 TRAE (bowel perforation). The most common grade ≥3 AEs were hyponatremia (*n*=4), infection (*n*=2), and hypertension (*n*=2).

The CARACAS trial is the first randomized clinical trial evaluating the role of immunotherapy in SCCA. Sixty previously treated patients with advanced disease were recruited to an open-label, "pick the winner," multicenter randomized phase II trial, and randomly assigned to avelumab, an anti-PD-L1, plus cetuximab or to avelumab alone [34]. The primary endpoint was ORR, which was 17% in the combination arm vs. 10% in the monotherapy arm, with a DCR of 57% vs. 50%, respectively. Median PFS was 3.9 months vs. 2.0 months, and OS data were not yet mature at the date of presentation. Skin and subcutaneous disorders were the most common AEs in cetuximab arm (87%), and fatigue was in the monotherapy arm (17%). Two patients (7%) in the combination arm permanently interrupted the treatment due to TRAEs, while no permanent interruptions secondary to TRAEs occurred in the monotherapy arm.

Ongoing clinical trials

Immunotherapeutic approaches are the main strategy being explored in the ongoing clinical trials in SCCA (Table 2). Based on the promising findings of ICIs in chemorefractory patients derived from single-arm phase II studies, RCTs have been designed to evaluate the efficacy of PD-1/PD-L1 inhibitors combined with chemotherapy in the first-line therapy. Thus, the backbone carboplatin plus paclitaxel has been evaluated both with retifanlimab (NCT04472429) and nivolumab (NCT04444921), and the triplet regimen modified DCF (docetaxel, cisplatin, 5-FU) has also been combined with atezolizumab in a randomized phase II study (NCT03519295) (Table 2). The strategy to combine anti-PD-1 with anti-CTLA-4 has also been tested in a randomized fashion (NCT02314169), as well as the use of PD-1/PD-L1 inhibitors in locally advanced disease (NCT03233711, NCT03357757).

Table 2. Ongoing clinical trials evaluating immunotherapeutic approaches in SCCA*

Population	Intervention	Control arm	ClinicalTrials.gov identifier
Phase I			
Metastatic/recurrent	PDS0101 + M7824 + NHS-IL12	-	NCT04287868
Advanced	XmAb20717	-	NCT03517488
Surgically unresectable or metastatic /HIV+	Nivolumab + ipilimumab	-	NCT02408861
Single-arm phase II			
Advanced	Avelumab + valproic acid	-	NCT03357757
Metastatic	Pembrolizumab	-	NCT02919969
Surgically unresectable or metastatic	Pembrolizumab	-	NCT02628067
Randomized phase II			
Locally advanced	Durvalumab + mitomycin + 5FU with RT	Mitomycin + 5FU with RT	NCT04230759
Metastatic	Nivolumab + ipilimumab	Nivolumab	NCT02314169
Metastatic or unressectable	mDCF + atezolizumab	mDCF	NCT03519295
Phase III			
Surgically unresectable or metastatic	Carboplatin + paclitaxel + nivolumab (followed by maintenance) 2:1 randomization	Carboplatin + Paclitaxel	NCT04444921
Surgically unresectable or metastatic	Carboplatin + paclitaxel + retifanlimab (followed by maintenance) 1:1	Carboplatin + Paclitaxel + Placebo	NCT04472429
Advanced	Anti-PD-1/PD-L1 1 year	Anti-PD-1/PD-L1 until disease progression	NCT04157985
High risk stage II-IIIB (after treatment)	Nivolumab	Observation	NCT03233711

*Active and recruiting on March 12, 2021
Abbreviations: *PD-1*, programmed cell death-1; *PD-L1*, programmed cell death-ligand-1; *5FU*, 5-fluorouracil; *RT*, radiation therapy; *mDCF*, modified docetaxel, cisplatin, 5-fluorouracil

Emerging strategies

The transfusion of lymphocytes, referred to as adoptive T cell therapies, has been tested in advanced SCCA, and it has demonstrated promising findings in pilot studies, mainly in those involving the modification of TCR (T cell receptors) and the creation of CAR (chimeric antigen receptors). The efficacy and safety of autologous genetically engineered T cells expressing a T cell receptor directed against HPV16 E6 (E6 TCR T cells) were evaluated in a first-in-human phase I/II study involving previously treated patients with metastatic HPV16-

positive cancer from any primary tumor site [35]. Patients also received a conditioning chemotherapy regimen and systemic aldesleukin. The expression of HLA-A*02:01 was an inclusion criterion. A total of twelve patients were included, of which four had SCCA. The only 2 out of 12 patients who reached partial response by RECIST 1.0 had SCCA. Apart from transient cytopenias secondary to the lymphocyte-depleting conditioning regimen, the treatment was well tolerated, with no acute toxicities to cell infusion or cytokine storm. Likewise, no autoimmune adverse events or off-target toxicities attributable to E6 TCR T cells were observed. Similar study was recently presented, but with autologous genetically engineered T cells expressing a TCR against HPV16 E7 (E7 TCR T cells) [36]. Six out of twelve patients presented objective response, which lasted from 3 to 9 months. Responders included patients with vulvar, SCCA, head and neck, and cervical cancer, of which four had been previously exposed to anti-PD-1 therapy.

Another immunotherapeutic approach is the use of bioengineered bacteria which secrete HPV-related antigens, with the potential to enhance tumor-specific responses and to reduce immune tolerance by neutralizing regulatory T cells and myeloid-derived suppressor cells within the tumor microenvironment [37–39]. Axalimogene filolisbac (ADXS11-001) consists of a live, irreversibly attenuated (prfA-deficient), and nonpathogenic strain of the intracellular bacterium *Listeria monocytogenes* (Lm), which has been bioengineered to secrete an antigen-adjuvant fusion protein between listeriolysin O (LLO) and the HPV-16 E7 oncoprotein. Based on promising pilot studies [40, 41], a single-arm, multicenter, first-in-human phase II trial was developed, involving patients with persistent/recurrent, loco-regional, or metastatic SCCA [42]. Patients received ADXS11-001, 1×10^9 colony-forming units intravenously every 3 weeks. The study would proceed to full enrollment if ORR ≥ 10% or 6-month PFS rate ≥ 20%. From a total of 36 patients treated, 29 were evaluable for response, of which only one had partial response (3.4% ORR). The 6-month PFS rate was 15.5%. Grade 3 AEs were reported in 10 patients, with the majority being cytokine-release symptoms. One grade 4 adverse event (respiratory failure) was noted. No grade 5 adverse events occurred.

The strategy to combine vaccines with ICIs has also been recently explored, based on the hypothesis that the efficacy of vaccine-induced T cells may be amplified by the ICIs. A phase II trial of ISA 101, a synthetic long-peptide HPV-16 vaccine, plus nivolumab was developed to investigate the strategy in patients with previously treated advanced HPV-16+ cancer [43]. ISA101 100 mcg/peptide was given on days 1, 22, and 50, and nivolumab 3 mg/kg was given every 2 weeks for up to 1 year. A total of 24 patients were recruited, of which 22 had oropharynx cancer and one patient each with anal and cervical cancer. ORR, the primary endpoint, was 33% (8/24). All responders were patients with oropharynx cancer. Median PFS was 2.7 months and OS rate at 6 months was 74%. The treatment was safe, with only one patient each with grade 3 transaminase and grade 4 lipase elevation.

Drug conjugates are another strategy that have been recently explored in advanced malignancies. PEN-866 is a miniature drug conjugate which links a HSP90 (heat shock protein 90) binding small molecule to a SN-38 cytotoxic payload, based on the rationale that HSP90 is highly expressed in several solid tumors [44]. PEN-866 targets and binds to activated tumor HSP90 protein, releases its cytotoxic payload, and results in complete tumor regressions in

multiple xenograft models. A first-in-human phase I study evaluated 30 patients with progressive and advanced solid malignancies [44]. PEN-866 was given weekly (3 out of 4 weeks in a 28-day cycle). The most frequent TRAEs were nausea (50%), fatigue (43%), and diarrhea (40%). From the 26 patients evaluable for response, 1 patient with SCCA achieved a confirmed partial response. Decreased target lesion size was observed in 6 additional patients. Bispecific antibodies that simultaneously target the immune checkpoint receptors PD-1 and CTLA-4, such as XmAb20717, are also being investigated in a phase I study (NCT03517488).

Conclusions

SCCA is an HPV-related malignancy markedly sensitive to CRT, but patients with locally advanced disease (T3-4 and/or node-positive) still present high rates of disease recurrence, which is typically associated with high morbidity and mortality. Systemic therapy in SCCA is an unmet clinical need. Based on the first completed RCT recently published, the combination of carboplatin plus paclitaxel has become the standard of care, but further developments are needed. The efficacy of ICIs as monotherapy has been modest in an unselected population of patients, but approximately 1 out of 5 patients with advanced SCCA may derive a meaningful benefit from PD-1 inhibitors, which point out the need to identify predictive biomarkers. The current role of immunotherapy in the therapeutic management of SCCA is focused on the treatment of chemorefractory disease, but ongoing clinical trials exploring combinations of chemotherapy plus ICIs, anti-PD-1/PD-L1 plus anti-CTLA-4, and emerging immunotherapeutic approaches, such as adoptive T cell therapies, may bring practice-changing results in the next few years for the treatment of this challenging disease.

Declarations

Conflict of Interest

Alexandre A. Jácome declares that he has no conflict of interest. Van Karlyle Morris has received research funding (paid to his institution) from Bristol-Myers Squibb. Cathy Eng declares that she has no conflict of interest.

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- • Of importance
- •• Of major importance

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