Chapter 7
Treatment of Advanced Anal Cancer

Satya Das and Kristen Keon Ciombor

Abbreviations

5-FU	5-fluorouracil
AE	Adverse event
ASCC	Anal squamous cell carcinoma
CC	Cervical cancer
CI	Continuous infusion
CP-5-FU	Cisplatin plus 5-fluorouracil
CPAC	Carboplatin plus paclitaxel
CP	Carboplatin
CR	Complete response
D	Day
DCF	Docetaxel, cisplatin, fluorouracil
DCR	Disease control rate
DFS	Disease-free survival
EGFR	Epidermal growth factor receptor
FOLFOX	5-FU, oxaliplatin and leucovorin
FOLFIRI	5-FU, irinotecan and leucovorin
G	Grade
GGT	Gamma-glutamyltransferase
Gy	Gray
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IV	Intravenous
MAP	Mitomycin C, adriamycin and cisplatin
mASCC	Metastatic anal squamous cell carcinoma
m^2	Meters squared
mg	Milligram

S. Das · K. K. Ciombor (✉)
Division of Hematology/Oncology, Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: satya.das@vumc.org; Kristen.k.ciombor@vumc.org

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NCCN	National Comprehensive Cancer Network
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
RFA	Radiofrequency ablation
SD	Stable disease
TIL	Tumor-infiltrating lymphocytes
TRAE	Treatment-related adverse event
WT	Wild-type

Introduction

Metastatic anal squamous cell carcinoma (mASCC) is a rare disease whose incidence is rising annually in the United States. Patients with anal squamous cell carcinoma (ASCC) are diagnosed de novo with metastatic disease in 5–10% of cases, and another 10–20% of patients initially diagnosed with local disease ultimately relapse distantly [1, 2]. Five-year survival rates for mASCC patients are less than 30%, and there are few systemic treatment options which have been validated prospectively or in a comparative fashion. Most patients with adequate performance status receive platinum-based doublet therapy based on results from case reports or small case series, with cisplatin plus 5-fluorouracil (CP-5-FU), oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) or carboplatin plus paclitaxel (CPAC). After progression on first-line therapy, the later-line treatment options become even more limited. Recently, given the success of immunotherapy in other malignancies with human papillomavirus (HPV)-mediated oncogenesis, immune-modulating agents have become an area of great interest in mASCC [3, 4]. We will discuss existing chemotherapy, targeted therapy, and immunotherapy data along with promising new treatments in development for mASCC in the subsequent paragraphs of this chapter.

Chemotherapy

Platinum-Doublet Therapy for Metastatic Anal Squamous Cell Carcinoma

One of the initial descriptions of the activity of CP-5-FU in mASCC was published by Khater and colleagues in the form of a two-patient case report [5]. Ajani and colleagues described three patients with hepatic metastases from anal primaries who were treated with intra-arterial floxuridine (5-FU being the catabolic end product of this drug) 100 mg/m^2 daily and cisplatin 30 mg/m^2 daily for 3 days per treatment cycle [6]. Two of the three patients had ongoing responses at 17 and 20 months,

respectively, while one patient had tumor progression after 4 months. Jaiyesimi and colleagues reported another case of patient with mASCC with necrotic inguinal lymph node recurrence who was treated with continuous infusion (CI) 5-FU 1000 mg/m^2 on days 1–5 (D1–D5) and cisplatin 100 mg/m^2 D1 every 21–28 days for 12 cycles [7]. The patient remained free of disease as of last reporting in 1992.

Faivre and colleagues described a single institution experience from the Institut Gustave Roussy in which 19 mASCC patients (10 with liver metastasis, 11 with lymph node metastasis, and 3 with pulmonary metastasis) received CI 5-FU 1000 mg/m^2 D1-D5 and cisplatin 100 mg/m^2 D2 every 28 days [8]. The median number of cycles patients received was 4, and 18 patients were evaluable for response. Overall response rate (ORR) was 66% with 1 complete response (CR) and 11 partial responses (PR). Disease control rate (DCR) was 89%. One-year survival was 62.2%, 5-year survival was 32.2% and median overall survival (OS) was 34.5 months. Patients developed grade 3/4 (G3/4) nausea in 30% of cases and neutropenia in 13% of cases. Haydon and colleagues published a case of a mASCC patient with extensive lung and liver metastases who achieved a CR with CP-5-FU [9]. The patient had treatment-naive p16-positive disease encompassing >50% of her liver, multiple pulmonary metastases, and intra-abdominal lymph nodes, along with an intact anal primary. She received 6 cycles of CP-5-FU with a CR seen on post-treatment CT scan. The patient remained disease free after 7 years at the time of publication.

Eng and coworkers presented a large single institution retrospective experience from MD Anderson Cancer Center looking at mASCC patient outcomes with systemic chemotherapy followed by either multidisciplinary management for curative intent or continuation of palliative chemotherapy. A total of 77 patients (4 with HPV, 3 with HIV) received 5-FU (CI 750 mg/m^2 D1-D5) plus cisplatin (75 mg/m^2 D1) every 4 weeks (42 patients), carboplatin (AUC 5 D1) plus paclitaxel (175 mg/m^2 D1) every 3 weeks, or a regimen not otherwise specified [10]. After a median follow-up of 42 months, median progression-free survival (PFS) was 7 months, and median OS was 22 months. When stratified by regimen, a non-statistically significant difference in median PFS was observed in favor of CP-5-FU compared to CPAC (8 months versus 4 months). ORR was 57% (all PRs) in the CP-5-FU treated patients, and DCR was 86%. ORR was 33% (all PRs) in the CPAC treated patients, while DCR was 54%. The experience of the mASCC patients treated with curative intent is described below in the oligometastatic disease section.

Kim and coworkers published a retrospective single-center experience from Moffitt Cancer Center in which 18 mASCC patients received CPAC (carboplatin AUC 5 or 6 on D1 and paclitaxel 175 mg/m^2 D1 every 3 weeks); 12 received this regimen in the first-line setting and 6 in the second-line setting [11]. Among patients who received this regimen first line, median OS was 12.1 months. ORR was 53% in all patients (3 CRs) and 69% among patients receiving first-line therapy. Grade 3 or 4 toxicities were observed in six patients with the most common ones being neutropenia and anemia. The EA2133/InterACCT study is a recently completed randomized phase II trial comparing first-line CP-5-FU versus CPAC in mASCC patients with a primary endpoint of ORR [NCT02051868]. This study was recently pre-

Table 7.1 Select published trials or retrospective patient series about the platinum-doublet chemotherapy experience in mASCC patients

Trial name or study authors	Treatment	P or R	Ongoing or completed	Number of patients	ORR (percent)	PFS (months)	OS (months)
Eng et al. [10]	CP-5-FU	R	Completed	42	57%; all PR	8	22 (entire cohort)
	CPAC	R	Completed	24	33%; all PR	4	22 (entire cohort)
Faivre et al. [8]	CP-5-FU	R	Completed	19	65%; all PR	4	N/A
Kim et al. [11]	CPAC	R	Completed	18	53%; 17% CR	N/A	12.1
EA2133	CP-5-FU vs CPAC	P	Ongoing	91	NA	N/A	N/A
Matsunaga et al. [13]	FOLFOX	R	Ongoing	1	100%; PR	N/A	N/A

CR complete response, *N/A* not applicable, *NR* not reached, *ORR* overall response rate, *OS* median overall survival, *P* prospective, *PFS* median progression-free survival, *PR* partial response, *R* retrospective, *vs* versus

sented and demonstrated an ORR of 57.1% for cisplatin/5-FU versus 59.0% for carboplatin/paclitaxel; however, OS was improved in the carboplatin/paclitaxel arm (mOS 20 vs 12.3 months, $p = 0.014$). With these results, investigation of the addition of targeted agents and/or immunotherapy for mASCC patients is anticipated [12].

Matsunaga and coworkers reported a single-patient case of a KRAS-mutant mASCC patient with liver and lung metastases who was treated with FOLFOX and bevacizumab every 2 weeks [13]. The patient received 22 doses of the combination and achieved a PR. At the time of the publication, the patient remained progression free. FOLFOX is a National Comprehensive Cancer Network (NCCN) category 2A recommendation for mASCC based on this report and extrapolation from data in metastatic rectal cancer.

Results from these series are summarized in Table 7.1.

Beyond Platinum-Doublet Therapy in Metastatic Anal Squamous Cell Carcinoma

Another studied chemotherapeutic regimen for the treatment of metastatic anal squamous cell carcinoma has been mitomycin C, adriamycin, and cisplatin (MAP) followed by bleomycin-CCNU, which was assessed in the ECOG 7282 trial (Table 7.2). Jhawer and coworkers reported the results from the phase II study where 20 patients with mASCC (15% treatment-naïve, 60% unknown prior treatment, if any) received MAP (mitomycin C 10 mg/m^2 D1, adriamycin 30 mg/m^2 D1, cisplatin 60 mg/m^2 D1) every 4 weeks for two cycles [14]. Thereafter, mitomycin C

Table 7.2 Select published trials and retrospective patient series about the platinum-doublet chemotherapy experience in mASCC patients

Trial name or study authors	Treatment	P or R	Ongoing or completed	Number of patients	ORR (percent)	PFS (months)	OS (months)
ECOG 7282 [14]	MAP plus BCNU	P	Completed	20	60%; all PR	8	15
Kim et al. [17]	DCF	P	Completed	66	89%; 45% CR	11	NR
Hainsworth et al. [16]	CPAC plus 5-FU	R	Completed	4	65%; 25% CR	26	NR
Alcindor et al. [18]	Paclitaxel	R	Completed	5	60%; all PR	3–8	4–20
Abbas et al. [19]	Paclitaxel	R	Completed	7	57%; all PR	NR	NR
Evans et al. [20]	Carboplatin	R	Completed	1	100%; PR	9	N/A

CR complete response, *N/A* not applicable, *NR* not reached, *ORR* overall response rate, *OS* median overall survival, *P* prospective, *PFS* median progression-free survival, *PR* partial response, *R* retrospective

was administered every 10 weeks, while adriamycin and cisplatin were administered every 5 weeks. Patients who developed progressive disease on MAP were eligible for bleomycin-CCNU; however, only two patients received this latter treatment. ORR was 60% (all PRs), median OS was 15 months and median PFS was 8 months. Fifty percent of patients experienced G3 hematologic adverse events (AEs), while 55% experienced G2 vomiting.

Kim and coworkers retrospectively assessed the efficacy of docetaxel 75 mg/m^2 D1, CP 75 mg/m^2 D1, and 5-FU 750 mg/m^2 D1-D5 (DCF) every 3 weeks in eight recurrent mASCC patients [15]. Six of the eight patients were HPV-positive, and all patients had initially received curative intent concurrent chemoradiation (CCR) with 5-FU and mitomycin C. Fifty percent of patients achieved an objective response, with four patients achieving a CR; the responding patients remained disease free as of the time of case series publication. Four patients experienced G3 toxicities but no patients experienced G4 toxicities. The most common G3 hematologic toxicities were anemia and neutropenia.

Hainsworth and coworkers assessed the combination of CPAC and 5-FU in metastatic squamous cell carcinoma patients of various origins in a phase II study [16]. Eighty percent of patients were treatment-naïve, while 20% received treatment in the second-line setting. Out of 60 patients, four had mASCC. Each patient received carboplatin AUC 6 on D1 and D22, 5-FU 225 mg/m^2 D1-D35 and paclitaxel 200 mg/m^2 D1 and D22 every 6 weeks for a maximum of four treatments. ORR was 65% (CR in 25%; CR 25% in the mASCC cohort), median PFS was 26 months and median OS was not reached in the entire cohort. The most frequent grade 3/4 toxicities experienced by patients in the study included leukopenia (48%), mucositis (28%) and diarrhea (17%).

Recently, Kim and associates published results from the Epitopes-HPV02 study [17]. In this single-center phase II study, mASCC patients or those with recurrent unresectable disease were treated with two different regimens of docetaxel, cisplatin and fluorouracil (DCF). Sixty-six patients were randomized to either standard DCF (75 mg/m^2 docetaxel D1, 75 mg/m^2 cisplatin D1 and 750 mg/m^2 of 5-FU D1-D5 every 3 weeks) or modified DCF (40 mg/m^2 docetaxel D1, 40 mg/m^2 cisplatin D1 and 1200 mg/m^2 of 5-FU D1-D2 every 2 weeks). The choice of which regimen to give patients was guided by age; patients >75 years old received modified DCF, and patients <75 years old received standard dosing DCF. The primary endpoint of the study was 12 month PFS post-cycle 1 of DCF. This primary endpoint of this study was met, with 47% of patients alive and progression-free at 12 months (minimum threshold for study to be deemed positive was 17%). A total of 61% of the patients who received standard DCF were progression-free at 12 months, while 60% of patients treated with the modified regimen were progression free at that timepoint. Median PFS and OS in all patients were 11 months and not reached, respectively. ORR in the entire cohort was 89%, with 45% of patients achieving CR. Adverse event profile clearly favored the modified regimen with reduced incidence of G3 neutropenia, anemia, vomiting, mucositis, diarrhea, or asthenia. No patients in the modified DCF arm experienced G4 febrile neutropenia events or non-hematologic events, compared to 14% and 8%, respectively, in the standard DCF arm.

Single-agent chemotherapy approaches that have been utilized in mASCC patients, either in the first-line setting for poor risk patients or after disease progression with first-line therapy, include paclitaxel, irinotecan and carboplatin [18–20]. Alcindor and associates reported findings from a five-patient mASCC case series from McGill University Health Centre [18]. Three patients were treated with paclitaxel 175 mg/m^2 every 3 weeks in the second-line setting after progression on CP-5-FU, while the other two patients received the agent in the first-line setting. Sixty percent of patients experienced PR, with disease control lasting from 3 to 8 months. Survival for these patients ranged from 4 to 20 months. Another case series from Abbas and associates looked at the experience of seven mASCC patients treated with weekly paclitaxel 80 mg/m^2 (3 out of 4 weeks) post-progression on CP-5-FU [19]. Fifty-seven percent of patients achieved radiographic response with duration of disease control between 4 and 6 months in responding patients. Patients who achieved PR had a median OS between 12 and 14 months. Evans and associates reported activity of single-agent carboplatin in a mASCC patient who progressed with pulmonary involvement 5 months after completing primary therapy with 5-FU-/mitomycin-based chemoradiation [20]. The patient received 600 mg of carboplatin every 4 weeks for six treatments. He achieved a PR after three treatments which persisted for 9 months.

Results from these series are summarized in Table 7.2.

Targeted Therapy

Anti-EGFR Antibodies in the Treatment of Metastatic Anal Squamous Cell Carcinoma

RAS (KRAS and NRAS) and BRAF mutations have been reported in 4–5% of ASCC patients, while other retrospective analyses suggest the frequency of these mutations is even lower [21, 22]. Given the rarity of RAS and BRAF mutations, along with the prevalence of epidermal growth factor receptor (EGFR) overexpression (roughly 90%) in ASCC, there appears to be a biologic rationale for EGFR inhibitors such as cetuximab or panitumumab in this disease [23].

Phan and Hoff reported their experience of a single mASCC patient treated with irinotecan plus cetuximab [24]. This patient was initially treated with concurrent CP-5-FU and radiation in the local setting but recurred distantly in multiple lymph node stations both within and outside of the pelvis. She received carboplatin and docetaxel with a mixed response and then was switched to single agent irinotecan 350 mg/m^2 every 3 weeks. She progressed in her right inguinal lymph node basin with worsening lower extremity edema and was subsequently switched to irinotecan 180 mg/m^2 every 2 weeks and cetuximab 250 mg/m^2 weekly (after a loading dose of 400 mg/m^2). She experienced PFS of 8 months with the regimen. Lukan and colleagues published their experience in seven mASCC patients treated with cetuximab; six of these patients received it weekly (250 mg/m^2 after a loading dose of 400 mg/m^2) along with irinotecan (100 mg/m^2), while one received cetuximab alone [25]. Tissue from all seven patients was retrospectively assessed for RAS mutational status. Among the five cetuximab-treated wild-type (WT) RAS patients, mean PFS was 7.5 months. Three of the five patients achieved a PR with one patient still in PR after 3.5 months of follow-up. All five patients who achieved disease control developed at least a grade 1 skin rash, while both nonresponders did not have any rash. No patients experienced G3/G4 toxicities. Both patients treated with cetuximab whose tumors were RAS mutant progressed rapidly.

Klimant and Markman also document the experience of two other mASCC patients who were treated with the combination of irinotecan and cetuximab with the same dosing schedule as above [26]. The first patient initially had locoregional disease treated with cisplatin plus capecitabine-based radiation. After two local recurrences, the patient recurred distantly at the ureter. Molecular profiling was performed; once WT RAS and BRAF status were confirmed, she was treated with irinotecan and cetuximab. The patient experienced a PFS of 17 months with the regimen. The second patient was initially treated with 5-FU-/mitomycin-based chemoradiation for locally advanced ASCC. At her first recurrence, she received cisplatin and paclitaxel for 7 months and achieved PFS for 5 years. After another

inguinal recurrence that was managed surgically, at the time of her third recurrence (also in inguinal lymph nodes), she was treated with irinotecan plus cetuximab which resulted in PFS of 14 months.

The largest series of mASCC patients treated with cetuximab was published by Rogers and colleagues [27]. Seventeen patients received cetuximab or panitumumab in the second- or third-line setting in combination with a variety of chemotherapy backbones including CP-5-FU, CP-vinorelbine, irinotecan, CPAC, CP-capecitabine or docetaxel. Seventy-one percent of patients had been treated with concurrent chemoradiation for locally advanced disease initially, while 29% presented with metastatic disease at diagnosis. Ninety-four percent of patients had received CP-5-FU or CPAC in the first-line setting. Thirty-five percent of patients achieved a PR and 59% of patients achieved disease control with the addition of either anti-EGFR antibody. Median PFS was 7.3 months and median OS was 24.7 months in all patients; patients who achieved disease control had a median PFS of 12.7 months and a median OS of 33.7 months.

Other published series have reported mASCC patient outcomes with later line cetuximab pairings including with mitomycin or 5-FU, leucovorin and irinotecan (FOLFIRI) [28, 29]. Based on the preceding retrospective data, there may be a role for anti-EGFR directed antibodies in RAS WT mASCC after progression on first-line platinum-doublet chemotherapy. The question of whether cetuximab or panitumumab can prospectively demonstrate benefit in the later-line settings and then potentially be evaluated in the first-line setting remains to be determined.

Results from these series are summarized in Table 7.3.

Table 7.3 Select retrospective patient series about the anti-epidermal growth factor receptor (EGFR) antibody experience in mASCC patients

Trial name or study authors	Treatment	P or R	Ongoing or completed	Number of patients	ORR (percent)	PFS (months)	OS (months)
Lukan et al. [25]	Cetuximab plus irinotecan	R	Completed	5	60%; all PR	7.5 (mean)	NR
Klimant et al. [26]	Cetuximab plus irinotecan	R	Completed	2	100%; all PR	15.5	N/A
Rogers et al. [27]	Cetuximab or Panitumumab ± various chemotherapy	R	Completed	17	35%; all PR	7.3	24.7

N/A not applicable, *NR* not reached, *ORR* overall response rate, *OS* median overall survival, *P* prospective, *PFS* median progression-free survival, *PR* partial response, *R* retrospective

Immunotherapy for the Treatment of Metastatic Anal Squamous Cell Carcinoma

There is a strong basis for immunotherapy in mASCC as the disease is characterized by immune dysregulation, which promotes unchecked HPV-driven oncogenesis (85–90% of cases) [30]. The HPV oncoproteins E6 and E7 promote anti-tumor host responses and stimulate infiltration by T lymphocytes. Circumstances such as receipt of organ transplant, autoimmune disease and HIV positivity are all well-known risk factors for ASCC development [31].

Checkpoint Inhibitors

The success of checkpoint inhibitors in other HPV-mediated metastatic squamous cell cancers incited efforts to investigate the efficacy of nivolumab or pembrolizumab in mASCC patients. Morris and colleagues reported findings from NCI 9673, a multicenter phase II study of nivolumab in progressive mASCC patients [32]. A total of 37 patients with a median of two prior therapies (86% with prior platinum-based therapy, 81% with prior chemoradiation in the localized disease setting) received nivolumab 3 mg/kg every 2 weeks. Patients received a median of six cycles of nivolumab with a median follow-up time of 10.1 months. Four out of 12 patients demonstrated a PR in the first phase of the two-stage design, meeting the prespecified threshold for minimal efficacy and allowing the trial to proceed. An additional 25 patients were recruited for the second phase of the trial. Nine of 37 patients (24%) achieved ORR with 2 CRs and 7 PRs. Seven of these patients achieved durable responses with a median duration of response (DOR) of 5.8 months. At the time of publication, the longest DOR for a patient was 10.4 months. Seventeen (47%) of patients achieved SD. Median PFS was 4.1 months and median OS was 11.5 months. Fourteen percent of patients experienced G3 AEs; however, no patients discontinued nivolumab due to drug-related toxicity. No HIV-positive patients experienced any G3 or G4 AEs. Thirteen patients (four responders, nine non-responders) underwent pre-treatment tumor biopsies. By immunohistochemistry, responding patients had higher baseline levels of CD8 T-cells, granzyme B and PD-L1 than non-responders. NCI 9673 has recently reopened to investigate the efficacy of nivolumab versus nivolumab plus the CTLA-4 inhibitor ipilimumab in mASCC patients.

Keynote-028 was a multi-cohort phase Ib study of single agent pembrolizumab in patients with tumors expressing PD-L1 >1%. In the anal cancer cohort, 43 mASCC patients were screened and 32 were found to have requisite PD-L1 expres-

sion, but eight were found to be ineligible. A total of 24 patients received pembrolizumab 10 mg/kg every 2 weeks, as reported by Ott and colleagues [33]. The primary endpoints for the study were safety and ORR. Fifty-two percent of enrolled patients had received two or more prior lines of therapy. Duration of median follow-up was 10.6 months, and median duration of therapy overall was 3.1 months. ORR was 17% (all PRs), while DCR was 59%; median duration of response was not reached. Two responders had ongoing responses at 9 months at the time of publication. Median PFS was 3 months and median OS was 9.3 months. Four G4 treatment-related AEs were observed, and there were no treatment-associated drug discontinuations.

Given the potential interest of utilizing checkpoint inhibitors in HIV-positive patients, the EUDRACT trial is an ongoing phase II study exploring the utility of the PD-L1 inhibitor durvalumab (administered 1500 mg IV every 4 weeks) in HIV-positive patients with rare tumors, including mASCC [NCT03094286]. The primary endpoint of the study is the number of patients who remain on durvalumab at 4 months, with secondary endpoints of ORR, PFS, and OS. Given the success of combining different classes of checkpoint inhibitors (i.e., CTLA-4 plus PD-1 inhibitors) in other tumors, nivolumab and ipilimumab are also being investigated in the HIV-positive population in an ongoing phase I trial through the AMC 095 consortium [NCT02408861]. In this study, HIV-positive patients, stratified by CD4 count >200 or between 100 and 200 with HIV-associated solid tumors (mASCC, Kaposi's sarcoma, and others) or classical Hodgkin lymphoma, will receive nivolumab at escalating doses along with ipilimumab at various frequencies. The primary endpoint of the study is safety, with an intent to determine the maximal tolerated dose (MTD) of the combination in this population. To our knowledge, combinations of PD-1 inhibitors and other checkpoints such as OX-40, LAG-3, or TIM-3 have not been prospectively studied in mASCC yet.

Adoptive T-Cell Transfer

Adoptive T-cell transfer involves the transfer of ex-vivo expanded antigen-specific lymphocytes, either autologous or engineered, into patients [34]. Some very encouraging results have been seen in metastatic cervical cancer, where nine refractory patients treated with a single infusion of autologous HPV tumor-infiltrating lymphocytes (TILs) (preceded by lymphodepleting cyclophosphamide and fludarabine) demonstrated an ORR of 33% [35]. Remarkably, two out of the three responses were CRs. Each enrolled patient underwent metastatic tumor biopsy, followed by TIL culturing with IL-2 based media. TIL cultures were then selected for optimal E6 and E7 reactivity and the chosen cultures were infused into patients following the lymphodepleting therapy.

Hinrichs and colleagues reported findings from a phase I/II study where the investigators engineered TIL to express a T-cell receptor targeting an HLA-A∗02:01-restricted epitope of E6 for patients with metastatic HPV16-positive carcinoma

[36]. Of 12 patients who received escalating doses of cells, four had mASCC. No patients suffered from dose limiting toxicities (DLT) or cytokine storm, and two of the mASCC patients achieved PRs lasting 6 and 3 months, respectively.

Vaccines

Therapeutic vaccines for mASCC remain an area of promise given the central role humoral immunity plays in stimulating T-cell-mediated responses which can clear HPV. The E6 and E7 oncoproteins in HPV are expressed constitutively, unsuccessfully masked and represent an ideal target [37]. A *Listeria*-based vaccine Lm-LLO-E7, which secretes the HPV16 E7 antigen fused to a non-hemolytic piece of the protein listeriolysin O (LLO), demonstrated promise in a phase I study in metastatic cervical cancer (mCC) patients [38]. In this study, 15 patients with recurrent or progressive mCC received escalating doses of the vaccine given at week 1 and week 4 intervals. All patients experienced flu-like symptoms and 40% experienced G3 treatment-related AEs (TRAEs). The most common G3 TRAEs were pyrexia, elevated GGT and elevated liver enzymes; however, no patients discontinued treatment due to AE. Although this study was not designed to assess efficacy, seven patients experienced SD. Of these seven patients, four had a decrease in tumor size which did not meet criteria for PR. Three patients underwent pre- and post-vaccination quantification of E7-specific T-cell responses via the ELISpot assay; only one of these patients demonstrated a specific T-cell response after the second vaccine dose. Based on these results, a phase II trial with the trademark Advaxis Lm-LLO-E7 vaccine (ADXS11-001) in persistent or recurrent ASCC and mASCC is underway [NCT02399813]. The framework of this study, also known as the FAWCETT trial, has been presented [39].

DPX-E7 represents another peptide-based vaccine composed of amino acids 11 through 19 of the viral oncoprotein HPV subtype 16 E7 (HPV16-E7 11-19). It is being explored in a phase Ib/II study in combination with cyclophosphamide in HLA-A∗02 positive patients with refractory or metastatic HPV-positive cervical cancer, ASCC and head and neck cancer [NCT02865135]. Cyclophosphamide depletes CD4 positive Foxp3 positive Treg cells, which play a crucial role in dampening anti-tumor response mediated by other effector lymphocyte subsets [40].

Another vaccine approach being explored in metastatic squamous cell cancers, including mASCC, is the combination of an mRNA-based vaccine against HPV16 antigens and an agonist antibody targeting CD40 [HARE-40]. CD40 is a member of the TNF superfamily expressed of several antigen-presenting cells (APC); preclinical work suggests activating CD40-positive dendritic cells greatly stimulates the amplitude of vaccine induced T-cell responses [41]. A phase I study previously demonstrated the safety of the anti-CD40 agonist (Anti-CD40 IS-Ab ChiLob7/4) [42]. The personalized cancer vaccine RO7198457 is being explored as monotherapy or in combination with the PD-L1 inhibitor atezolizumab across several disease sites, including mASCC, in a phase Ia/Ib study [NCT03289962].

Results from these series are summarized in Table 7.4.

Table 7.4 Select published trials and ongoing studies about utilizing immunotherapy (checkpoint inhibitors, TIL therapy, vaccines) in mASCC patients

Trial name or study authors	Treatment	P or R	Ongoing or completed	Number of patients	ORR (percent)	PFS (months)	OS (months)
NCI 9673	Nivolumab	P	Completed	37	24%; 3% CR	4.1	11.5
Keynote 028	Pembrolizumab	P	Completed	24	17%; all PR	3	9.3
EURDACT	Durvalumab	P	Ongoing	N/A	N/A	N/A	N/A
NCT02408861	Nivolumab plus Ipilimumab	P	Ongoing	N/A	N/A	N/A	N/A
Hinrichs et al. [36]	TIL targeting HLA-A∗02:01-restricted epitope of E6	P	Completed	4	50%; all PR	NR	NR
FAWCETT	ADXS11–001 (lm-LLO-E7) vaccine	P	Ongoing	55	N/A	N/A	N/A
HARE-40	mRNA vaccine against HPV16 antigens ± anti-CD40 antibody	P	Ongoing	44	N/A	N/A	N/A
NCT03289962	RO7198457 ± atezolizumab	P	Ongoing	567 (multiple disease sites)	N/A	N/A	N/A

CR complete response, *N/A* not applicable, *NR* not reached, *ORR* overall response rate, *OS* median overall survival, *P* prospective, *PFS* median progression-free survival, *PR* partial response, *R* retrospective

Oligometastatic Disease in Anal Squamous Cell Carcinoma

Local management of limited oligometastatic disease from lower gastrointestinal tumors such as colorectal adenocarcinoma has changed the trajectory of the disease and improved OS for many patients. Whether this same principle can be utilized for patients with mASCC with limited sites of involvement remains unclear. Several studies suggest the potential benefit from such an approach. Eng and colleagues reported 33 patients who underwent curative intent multidisciplinary management after systemic therapy for their metastatic disease. Of these patients, 58% either underwent resection of their metastasis or radiofrequency ablation (RFA), while 42% underwent chemoradiation [10], with extent of metastasis to qualify for this approach not detailed. Overall, 50% of the radiation-sensitizing regimens involved CP-5-FU, while 28% involved CPAC or 5-FU/capecitabine alone. Of the 19 patients who underwent resection or RFA, 16 underwent surgical resection (9 in the liver, 2 in the lungs, 5 in the lymph nodes). Median PFS in mASCC patients treated with curative intent after initial systemic therapy was 16 months compared to 5 months in patients treated with palliative chemotherapy alone ($p < 0.001$). Median OS was 53 months for mASCC patients treated with curative intent and 17 months for mASCC patients treated with palliative intent ($p < 0.001$).

Rogers and associates presented a case series of five mASCC patients with oligometastatic disease (four metachronous, one synchronous) who were managed with concurrent chemoradiation (CCR) and other locoregional treatment approaches (radiofrequency ablation, surgery) [43]. Four of the five patients received systemic therapy with single agent 5-FU (one patient) or multi-agent combinations (1 with CPAC, 2 with CP-5-FU) with or without anti-EGFR antibodies and achieved treatment response prior to chemoradiation. The five patients achieved disease-free intervals ranging from 14 to 32 months. Hodges and associates presented another case series of six newly diagnosed mASCC patients with para-aortic and inguinal-node-only distant involvement treated with CCR [44]. Patients received 6 weeks of intensity-modulated radiation along with CP-5-FU 5 days per week. The primary tumor was treated to 57 Gy, while involved lymph nodes were treated to 55 Gy. After a median follow-up of 25 months, none of the patients had any local recurrence at sites initially involved with disease. Two patients developed metastatic disease in the liver, one at 4 months and one at 34 months after completing CCR. Three-year OS for all patients was 63%. A total of four patients developed nausea/vomiting and diarrhea which required hospitalization, and five patients developed G2 skin toxicity.

Pawlik and associates published a retrospective analysis from eight large hepatobiliary centers which explored the impact of liver metastasectomy and/or RFA on OS and disease-free survival with metastatic squamous carcinomas [45]. A total of 52 patients, 27 of who had mASCC, were included in the analysis. Sixty-seven percent of the mASCC patients presented with metachronous metastatic disease to the liver; median number of metastases was one, and the median size of the metastases was 5.8 cm in this group. Seventy percent of patients with mASCC were

treated with CCR in the local setting. Eighty-nine percent of mASCC patients underwent resection of their liver lesions, while 7.4% underwent surgery plus RFA and 3.7% underwent RFA alone. Seventy-four percent of the mASCC patients received pre-resection chemotherapy (regimens and frequency unspecified), with 80% of patients achieving disease control (40% PR, 40% SD). Sixty-three percent of mASCC patients received postoperative adjuvant therapy. Patients with mASCC had a median DFS of 9.6 months compared to 9.8 months in the non-mASCC cohort ($p = 0.43$). Twenty-two percent of patients experienced recurrent disease in the liver, 19% experienced both intrahepatic and extrahepatic recurrences, and 15% of patients in the mASCC cohort recurred elsewhere. There was no difference in 5-year survival between mASCC and non-mASCC cohorts (22.9% and 18.4%, $p = 0.75$). Median OS of all patients was 22.3 months.

Joe and associates describe the case of a p16-positive mASCC patient with bulky local disease along with liver, bone, and lymph node metastases where palliative CCR to the primary site elicited an abscopal immune effect leading to CR of all other tumor sites [46]. The patient received 54 Gy in radiation to the primary tumor and 50.4 Gy to the nodal and bony metastases, along with sensitizing chemotherapy with capecitabine (750 mg/m^2 twice daily on days of radiation) and mitomycin 10 mg/m^2 (D1 and D28). Within 6 weeks, the patient's bulky primary disease and mesorectal nodes were no longer clinically appreciated. Four weeks after completion of CCR, CT imaging demonstrated regression of the original 16 liver masses with only one 5 mm liver mass visible. At 4 months, no visible disease was noted on surveillance CT scans. Although the patient did receive chemotherapy and this may have influenced the disease response in the liver, the treatment effect was thought to exceed what would have been expected from chemotherapy alone. Retrospective staining of the patient's tumor tissue was performed to assess its immune signature and investigate the nature of the patient's complete response. Multiple regions of her tumor were infiltrated by CD8 and CD4 TILs. Intra-tumoral TILs expressed PD-1 more robustly than TILs found along the stromal interface.

Summary

Treatment of mASCC remains a challenge both in the United States and globally. The dearth of prospective evidence regarding chemotherapy, biologic and immunotherapy options, as well as a rising incidence of disease highlights the importance of ongoing investigative efforts to improve clinical outcomes for patients with mASCC. Platinum-doublet-based chemotherapy remains a fixture in treatment of this disease, and results from the InterAACT study demonstrate that the carboplatin/paclitaxel likely should serve as the optimal platinum-doublet backbone for future combination studies. Recent findings from the Epitopes-HPV02 study suggest DCF might be the most potent initial regimen in mASCC patients with more tolerable AEs utilizing a modified dosing regimen instead of standard dosing. A prospective study comparing DCF with the optimal platinum-doublet regimen would naturally be the next step to determine whether platinum-triplet or

platinum-doublet therapy is standard of care for mASCC patients. Anti-EGFR therapies such as cetuximab and panitumumab have a potential role in mASCC patients, given the limited number of RAS and BRAF mutations seen in this group. Furthermore, the efficacy signal suggested from retrospective data with biologics in the later-line setting raises the question of whether these therapies would be tolerable and effective in earlier lines of therapy. Immunotherapy with checkpoint inhibitors has demonstrated great promise in patients with other metastatic HPV-associated squamous malignancies as well as mASCC. Given the potential for durable responses and often tolerable side effects, checkpoint inhibitors are a welcome addition to treatment of mASCC patients who have previously received systemic therapy. The prospective data with nivolumab and pembrolizumab are encouraging, and ongoing studies with checkpoint inhibitor combinations and earlier lines of therapy will inform how benefit can be maximizes with these agents. Beyond checkpoint inhibitors, other immune-modulating strategies such as vaccines and adoptive T-cell transfer have demonstrated early promise in the treatment of mASCC. Oligometastatic ASCC patients are also a subset of great interest due to the potential ability to change their disease trajectory with durable responses after systemic therapy followed by locoregional treatment. Based on the data presented above, there appears to be potential to markedly improve PFS and OS in carefully selected patients within this group. Better understanding of the biological, genomic and immunological underpinnings of mASCC, as well as ongoing and anticipated prospective clinical trials, promise to move the field forward to improve clinical outcomes for patients with this disease.

References

1. Cancer stat facts: anal cancer. Available at https://seer.cancer.gov/statfacts/html/anus.html. Accessed 28 June 2018.
2. Das P, Bhatia S, Eng C, Ajani JA, Skibber JM, Rodriguez-Bigas MA, et al. Predictors and patterns of recurrence after definitive chemoradiation for anal cancer. Int J Radiat Oncol Biol Phys. 2007;68(3):794–800.
3. Ferris R, Blumenschein G, Fayette J, Guigay J, Colevas D, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375:1856–67.
4. Hollenbecque A, Meyer T, Moore K, Machiels JP, De Greve J, Lopez-Picazo J, et al. An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers. J Clin Oncol. 2017;35(15):S5504.
5. Khater R, Frenay M, Bourry J, Milano G, Namer M. Cisplatin plus 5-fluorouracil in the treatment of metastatic anal squamous cell carcinoma: a report of two cases. Cancer Treat Rep. 1986;70(11):1345–6.
6. Ajani J, Carrasco H, Jackson D, Wallace S. Combination of cisplatin plus fluoropyrimidine chemotherapy effective against liver metastases from carcinoma of the anal canal. Am J Med. 1989;87(2):221–4.
7. Jaiyesimi I, Pazdur R. Cisplatin and 5-fluorouracil as salvage therapy for recurrent metastatic squamous cell carcinoma of the anal canal. Am J Clin Oncol. 1993;16(6):536–40.
8. Faivre C, Rougier P, Ducreux M, Mitry E, Lusinchi A, Lasser P, et al. 5-fluorouracile and cisplatinum combination chemotherapy for metastatic squamous-cell anal cancer. Bull Cancer. 1999;86(10):861–5.

9. Haydon A, Tay R, Mak G, Shapiro J. Long survival (cure) to cisplatin/Infusional 5-Flurouracil in metastatic squamous cell anal cancer with extensive liver and lung metastases. Case Rep Cli Med. 2015;4(3):73–6.
10. Eng C, Chang G, You N, Das P, Rodriguez-Bigas M, Xing Y, et al. The role of systemic chemotherapy and multidisciplinary management in improving the overall survival of patients with metastatic squamous cell carcinoma of the anal canal. Oncotarget. 2014;5(22):1133–42.
11. Kim R, Byer J, Fulp WJ, Mahipal A, Dinwoodie W, Shibata D. Carboplatin and paclitaxel treatment is effective in advanced anal cancer. Oncology. 2014;87(2):125–32.
12. Rao S, Sclafani F, Eng C, et al. InterAACT: a multicentre open label randomised phase II advanced anal cancer trial of cisplatin (CDDP) plus 5-fluorouracil (5-FU) vs carboplatin (C) plus weekly paclitaxel (P) in patients (pts) with inoperable locally recurrent (ILR) or metastatic treatment naïve disease – an International Rare Cancers Initiative (IRCI) trial. Presented at ESMO 2018, Munich, Germany.
13. Matsunaga M, Miwa K, Oka Y, Nagasu S, Sakaue T, Fukahori M, et al. Successful treatment of metastatic anal canal adenocarcinoma with mFOLFOX6 + bevacizumab. Case Rep Oncol. 2016;9(1):249–54.
14. Jhawer M, Mani S, Lefkopoulou M, Hahn RG, Harris J, Catalano PJ, et al. Phase II study of mitomycin-C, adriamycin, cisplatin (MAP) and bleomycin-CCNU in patients with advanced cancer of the anal canal: an eastern cooperative oncology group study E7282. Investig New Drugs. 2006;24(5):447–54.
15. Kim M, Jary M, Mansi L, Benzidane B, Cazorla A, Demarchi M. DCF (docetaxel, cisplatin and 5-fluorouracil) chemotherapy is a promising treatment for recurrent advanced squamous cell anal carcinoma. Ann Oncol. 2012;24(12):3045–50.
16. Hainsworth JD, Burris HA 3rd, Meluch AA, Baker MN, Morrissey LH, Greco FA. Paclitaxel, carboplatin, and long-term continuous infusion of 5-fluorouracil in the treatment of advanced squamous and other selected carcinomas: results of a phase II trial. Cancer. 2001;92(3):642–9.
17. Kim S, Francois E, Andre T, Samalin E, Jary M, Hajbi F, et al. Docetaxel, cisplatin, and fluorouracil chemotherapy for metastatic or unresectable locally recurrent anal squamous cell carcinoma (epitopes-HPV02): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2018;19(8):1094–106.
18. Alcindor T. Activity of paclitaxel in metastatic squamous anal carcinoma. Int J Color Dis. 2008;23(7):717.
19. Abbas A, Nehme E, Fakih M. Single-agent paclitaxel in advanced anal cancer after failure of cisplatin and 5-fluorouracil chemotherapy. Anticancer Res. 2011;31(12):4637–40.
20. Evans TR, Mansi JL, Glees JP. Response of metastatic anal carcinoma to single agent carboplatin. Clin Oncol. 1993;5(1):57–8.
21. Morris V, Rao X, Pickering C, Foo WC, Rashid A, Eterovic K, et al. Comprehensive genomic profiling of metastatic squamous cell carcinoma of the anal canal. Mol Cancer Res. 2017;15(11):1542–50.
22. Gardini A, Capelli L, Ulivi P, Giannini M, Freier E, Tamberi S, et al. KRAS, BRAF and PIK3CA status in squamous cell anal carcinoma (SCAC). PLoS One. 2014;9(3):e92071.
23. Paliga A, Onerheim R, Gologan A, Spatz A, Vuong T. EGFR expression in invasive anal carcinoma. J Clin Oncol. 2011;29(4):S412.
24. Phan L, Hoff PM. Evidence of clinical activity for Cetuximab combined with irinotecan in a patient with refractory Anal Canal squamous-cell carcinoma: report of a case. Dis Colon Rectum. 2007;50(3):395–8.
25. Lukan N, Ströbel P, Willer A, Kripp M, Dinter D, Mai S, et al. Cetuximab-based treatment of metastatic anal cancer: correlation of response with KRAS mutational status. Oncology. 2009;77(5):293–9.
26. Klimant E, Markman M. Management of two cases of recurrent anal carcinoma. Case Rep Oncol. 2013;6(3):456–61.
27. Rogers JE, Ohinata A, Silva NN, Mehdizadeh A, Eng C. Epidermal growth factor receptor inhibition in metastatic anal cancer. Anti-Cancer Drugs. 2016;27(8):804–8.
28. Khawandanah M, Baxley A, Pant S. Recurrent metastatic anal cancer treated with modified paclitaxel, ifosfamide, and cisplatin and third-line mitomycin/cetuximab. J Oncol Pharm Prac. 2015;21(3):232–7.

29. Barmettler H, Komminoth P, Schmid M, Duerr D. Efficacy of Cetuximab in combination with FOLFIRI in a patient with KRAS wild-type metastatic anal cancer. Case Rep Oncol. 2012;5(2):428–33.
30. Meulendijks D, Tomasoa NB, Dewit L, Smits PM, Bakker R, Van Velthuysen ML, et al. HPV-negative squamous cell carcinoma of the anal canal is unresponsive to standard treatment and frequently carries disruptive mutations in TP53. Br J Cancer. 2015;112:1358–66.
31. Shridhar R, Shibata D, Chan E, Thomas C. Anal cancer: current standards in care and recent changes in practice. CA Cancer J Clin. 2015;65(2):139–62.
32. Morris VK, Salem ME, Nimeiri H, Iqbal S, Singh P, Ciombor K, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017;18(4):446–53.
33. Ott, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. Ann Oncol. 2017;28(5):1036–41.
34. Rosenberg S, Restifo N. Adoptive cell transfer as personalized immunotherapy for human cancer. Science. 2015;348(6230):62–8.
35. Stevanovic S, Draper L, Langhan M, Campbell T, Kwong ML, Wunderlich R, et al. Complete regression of metastatic cervical Cancer after treatment with human papillomavirus–targeted tumor-infiltrating T cells. J Clin Oncol. 2015;33(14):1543–55.
36. Hinrichs C, Doran S, Stevanovic S, Adhikary S, Mojadidi M, Kwong ML, et al. A phase I/II clinical trial of E6 T-cell receptor gene therapy for human papillomavirus (HPV)-associated epithelial cancers. J Clin Oncol. 2017;35(15):S3009.
37. Tan S, De Vries EG, Van Der Zee AG, De Jong S. Anticancer drugs aimed at E6 and E7 activity in HPV-positive cervical cancer. Cur Cancer Drug Tar. 2012;12(2):170–84.
38. Maciag PC, Radulovic S, Rothman J. The first clinical use of a live-attenuated listeria monocytogenes vaccine: a phase I safety study of Lm-LLO-E7 in patients with advanced carcinoma of the cervix. Vaccine. 2009;27(30):3975–83.
39. Fakih M, O'Neil B, Chiorean EG, Hochster H, Chan E, Mauro D, et al. Phase II study of ADXS11-001 in patients with persistent/recurrent, locoregional or metastatic squamous cell carcinoma of the anorectal canal. J Clin Oncol. 2016;34(4.):suppl):TPS786.
40. Zhao J, Cao Y, Lei Z, Yang Z, Zhang B, Huang B. Selective depletion of CD4+CD25+Foxp3+ regulatory T cells by low-dose cyclophosphamide is explained by reduced intracellular ATP levels. Cancer Res. 2010;70(12):4850–8.
41. Ma D, Clark E. The role of CD40 and CD40L in dendritic cells. Semin Immunol. 2009;21(5):265–72.
42. Johnson P, Challis R, Chowdury F, Gao Y, Harvey M, Geldart T, et al. Clinical and biological effects of an agonist anti-CD40 antibody. A Cancer Research UK phase I study. Clin Cancer Res. 2015;21(6):1321–8.
43. Rogers J, Crane C, Das P, Delclos M, Gould M, Ohinata A, et al. Definitive chemoradiation in oligometastatic squamous cell carcinoma of the anal canal. Gastrointest Cancer Res. 2014;7(2):65–8.
44. Hodges JC, Das P, Eng C, Reish AG, Beddar AS, Delclos ME, et al. Intensity-modulated radiation therapy for the treatment of squamous cell anal cancer with para-aortic nodal involvement. Int J Radiat Oncol Biol Phys. 2009;75(3):791–4.
45. Pawlik TM, Gleisner AL, Bauer TW, Adams RB, Reddy SK, Clary BM, et al. Liver-directed surgery for metastatic squamous cell carcinoma to the liver: results of a multi-center analysis. Ann Surg Oncol. 2007;14(10):2807–16.
46. Joe MB, Lum JJ, Watson PH, Tonseth RP, McGhie JP, Truong PT. Radiation generates an abscopal response and complete resolution of metastatic squamous cell carcinoma of the anal canal: a case report. J Gastrointest Oncol. 2017;8(6):E84–9.