Systemic therapy for recurrent or metastatic salivary gland malignancies

Ashish V. Chintakuntlawar*, Scott H. Okuno and Katharine A. Price

Abstract
Salivary gland carcinomas are notoriously resistant to therapy and no standard of care exists. Due to the rarity of these malignancies, various histologies, and wide ranging clinical behavior it has been difficult to standardize systemic therapy. We have reviewed clinical prospective studies in the last 15 years with salivary gland malignancies involving cytotoxic chemotherapy and biologic agents including targeted therapies such as anti-HER-2, anti-EGFR therapies, and therapies directed at c-kit. Although the results of most trials are modest at best, there has been an increase in studies for salivary cancer in recent years and there are several promising treatment approaches in evolution. Every effort should be made to treat salivary gland malignancies under a clinical protocol and/or at a large multidisciplinary practice with clinicians experienced in treating these malignancies.

Keywords: Salivary gland malignancy, Carcinoma, Systemic therapy, Chemotherapy, Targeted therapy, Immunotherapy, Hormone therapy, HER2 therapy

Abbreviations: ACC, Adenoid cystic carcinoma; CBR, Clinical benefit rate; EGFR, Epidermal growth factor receptor; FGFR, Fibroblast growth factor receptor; HDAC, Histone deacetylase; HER-2, Human epidermal growth factor receptor-2; MEC, Mucoepidermoid carcinoma; ORR, Overall response rate; OS, Overall survival; PDGFR, Platelet derived growth factor receptor; PR, Partial response; SDC, Salivary duct carcinoma; TKI, Tyrosine kinase inhibitor; VEGF, Vascular endothelial growth factor

Background
Salivary gland malignancies are morphologically and clinically varied neoplasms and account for approximately 5–7% of head and neck cancers. Salivary gland malignancies can occur throughout the upper aerodigestive tract but the majority of tumors occur in the parotid gland and other major salivary glands [1]. The heterogeneity of salivary malignancies is underscored by the World Health Organization classification, which categorizes these tumors into 24 subtypes with varying biologic characteristics, clinical behaviors, and survival outcomes [2].

Systemic therapy for salivary gland cancers has been a longstanding problem for medical oncologists. Many malignant salivary cancers are largely cured with surgery alone but oncologists routinely encounter such subtypes as adenoid cystic carcinoma (ACC), adenocarcinoma NOS, carcinoma ex-pleomorphic adenoma, mucoepidermoid carcinoma (MEC), and salivary duct carcinoma (SDC) in the recurrent and metastatic setting. The clinical behaviors of the various types of salivary cancers range from aggressive to indolent, with heterogeneity even within any given subtype, making treatment standardization a challenge. Regardless of the type of salivary cancer, the majority of patients with metastatic salivary gland cancer will succumb to the disease, and metastatic disease remains incurable.

Surgical resection is the cornerstone of treatment for salivary gland malignancies. Radiotherapy is often employed as adjuvant therapy for tumors deemed to be at high risk of recurrence or as definitive treatment when surgical resection is not feasible. The role of chemotherapy in the definitive treatment of salivary cancer remains to be defined. The potential benefit of adding platinum chemotherapy to adjuvant radiotherapy for high-risk salivary cancer is currently under investigation in RTOG 1008 (NCT01220583), and the results of this randomized trial will hopefully inform future management. For now, the use of chemotherapy in
the definitive management of salivary cancers remains up to the clinical judgment of the treating physician. The primary use of chemotherapy or systemic therapy is for patients with recurrent or metastatic disease for whom surgery or radiotherapy is not possible. Rigorous testing or standardization of systemic therapies in metastatic or recurrent salivary gland carcinomas is extremely difficult due to the rarity and heterogeneity of these tumors. In this review we discuss the current knowledge about therapeutic options for recurrent and metastatic salivary gland malignancies with a focus on cytotoxic chemotherapy and biologic agents tested in the last 15 years and a look towards future therapeutics.

**Literature search**

PubMed, Medline, and Ovid databases were searched for studies related to systemic therapy for salivary gland carcinomas; lymphomas were excluded. English language publications including reviews and abstracts from January 2001 to December 2015 were considered. The time frame was restricted as there is a comprehensive review of cytotoxic chemotherapy already published in 2006 [3]. References of the studies obtained were cross-referenced for additional studies. Only phase 2–3 studies were considered. Select prospective studies were included if patients were chosen based on specified inclusion criteria and if all patients were treated with a specific regimen in a standard fashion. Select case reports/series were included only for SDC as they are particularly clinically relevant. Retrospective studies and duplicate studies published as abstracts previously were excluded.

The following sections summarize key findings of recent clinical trials for cytotoxic chemotherapy, targeted and biologic agents, and combination therapies, with a brief discussion of hormone therapy for SDC.

**Cytotoxic chemotherapy**

**Combination therapy with platinum**

The prior review of chemotherapy for advanced salivary malignancies by Laurie et al. in 2006 reported variable modest response rates to cytotoxic chemotherapy and concluded that there is no standard of care cytotoxic chemotherapy. The most studied chemotherapeutic regimen was the historic salivary cancer regimen cyclophosphamide, doxorubicin, and cisplatin [3]. The authors concluded that there was no clear benefit for the use of triplet therapy over single agent regimens [4, 5]. We reviewed prospective studies from 2001 to 2015 investigating cytotoxic chemotherapy for all salivary gland tumors including ACC, adenocarcinoma NOS, and MEC, with the majority of trials using chemotherapeutic combinations with either cisplatin or carboplatin (Table 1). Almost half of the studies were restricted to ACC, but the other half included other histologic subtypes albeit in smaller numbers. Four studies in particular appear to show support for the use of platinum doublet therapy; all four studies included a mixed population of patients with salivary cancer, although ACC and adenocarcinoma predominated. One study by Airoldi et al. showed improved overall response with the combination of cisplatin and vinorelbine over vinorelbine alone (44 versus 20 %, respectively), and notably is one of the only studies with randomized data [6]. In addition, the objective response rate (ORR) as well as overall survival (OS) showed a trend towards statistical significance in favor of the combination arm. Another study investigating the

---

**Table 1** Studies with cytotoxic chemotherapy alone or in combination with biologic agents

| Author(s) (year) | Regimen | No of patients | Histology | Progression required | ORR | CBR | Median OS (months) |
|-----------------|---------|----------------|-----------|----------------------|-----|-----|-------------------|
| Airoldi et al. [6] | Vino vs Cis + Vino | 20 vs 16 | Ad (9), ACC (22), MEC (1), others (4) | Yes | 20 % vs 44 % | 65 % vs 81 % | 8.5 vs 10 |
| Gedlicka et al. [7] | Mitoxantrone + Cis | 14 | NR | No | 14 % | 79 % | 27 |
| Gilbert et al. [11] | Paclitaxel | 45 | Ad (17), ACC (14), MEC (14) | No | 18 % | 51 % | 12.5 |
| van Herpen et al.[12] | Gemcitabine | 21 | ACC (21) | No | 0 % | 52 % | NR |
| Ross et al. [10] | Epirubicin + Plat + SFU | 8 | ACC (8) | No | 12 % | 75 % | 27 |
| Laurie et al. [8] | Plat + Gemcitabine | 33 | Ad (8), ACC (10), MEC (4), others (11) | Yes<sup>a</sup> | 24 % | 82 % | 13.8 |
| Ghosal et al. [47] | Cis + Imatinib | 28 | ACC (28) | No | 11 % | 79 % | 35 |
| Argiris et al. [50] | Bor → Bor + Dox | 24 | ACC (24) | Yes | 0 % and 8 %<sup>b</sup> | 63 % and 58%<sup>b</sup> | 21 |
| Hitre et al. [49] | Cetuximab + Cis + SFU | 12 | ACC (12) | No | 42 % | 92 % | 24 |
| Airoldi et al. [9] | Cis + Vino | 60 | Ad (15), ACC (34) | Yes | 23 % | 57 % | 10<sup>c</sup> |

<sup>a</sup>not required for adenoid cystic carcinoma

<sup>b</sup>response rates for Bor and Bor + Dox combination respectively

<sup>c</sup>median survival for first-line patients only
combination of cisplatin plus mitoxantrone showed an ORR of 14% and a median OS of 27 months [7]. A third study by the National Cancer Institute of Canada Clinical Trials Group studied platinum and gemcitabine in patients with advanced salivary cancer with disease progression (not required for ACC patients) and reported that the ORR was 24% and the clinical benefit rate (CBR) was 82%. Four patients out of eight with adeno-carcinoma (3 per RECIST) had a partial response and one had a complete response [8]. Recently, a large cohort of 60 patients treated with cisplatin and vinorelbine showed an ORR of 23% with better responses seen in the first-line setting (31% first line versus 5% second line) [9]. Triplet therapy with platinum was reported in a small study by Ross et al. investigating the combination of cisplatin/carboplatin, epirubicin, and 5-flurouracil (5-FU) in eight patients with ACC, seven as first-line therapy [10]. Despite the addition of a third cytotoxic agent, the ORR was only 12%, further supporting the notion that triplet cytotoxic regimens have no clinical benefit for metastatic salivary cancers. Even though the ORR was modest, the median OS was still 27 months underscoring the often indolent clinical behavior of metastatic ACC and the dual challenges of studying systemic therapy and having transient disease response translate into a meaningful survival advantage.

**Single agent cytotoxic chemotherapy**

With the advent of interest in biologic and targeted therapies, single agent chemotherapy trials have become rare. In 2006, an Eastern Cooperative Oncology Group study of single agent paclitaxel showed some activity (18%) in salivary gland carcinomas but all objective responses were seen in patients with adenocarcinoma or MEC (29% adenocarcinoma and 21% MEC); no objective responses were seen in patients with ACC. Despite this differential response, the OS was comparable for all subtypes, again highlighting the fact that systemic therapy has no known survival benefit for metastatic salivary cancer [11]. A second study of single agent gemcitabine exclusively in patients with ACC was completely negative with no objective responses seen [12].

**Biologic agents**

The limited utility and efficacy of cytotoxic chemotherapy have compelled the need for systematic study of alternative therapies for advanced salivary gland carcinomas. With the knowledge that salivary gland carcinomas express various potential targets such as the epidermal growth factor receptor (EGFR) [13, 14], c-kit [15], and human epidermal growth factor receptor-2 (HER-2) [16], numerous trials of biologic agents have been conducted since 2003 (Table 2).

**HER-2 directed therapy**

Results of HER-2 directed therapy for patients with recurrent or metastatic salivary gland cancer have been disappointing to date, with the notable exception being patients with HER-2-positive SDC [17]. One the first studies that attempted to explore the activity of trastuzumab in an unselected population of advanced salivary gland cancers was stopped early when it was found that HER-2 positive salivary gland carcinomas are actually very rare. Fourteen patients were ultimately enrolled (7 ACC) with a single response seen in a patient with MEC [18]. Lapatinib was also studied in salivary gland carcinomas with no objective responses seen. Of note, stable disease was reported in 78% of patients and progressive disease was required prior to trial enrollment [19].

**EGFR-directed therapy**

EGFR overexpression is seen in salivary gland carcinomas [13, 14] and hence single agent cetuximab and gefitinib were studied in two negative phase 2 trials. Locati et al. enrolled 30 patients (23 ACC) with no objective responses noted with single agent cetuximab [20]. Similarly, a study by Jakob et al. in an unselected population of patients with advanced salivary malignancies reported no objective responses to gefitinib [21]. Given the complete lack of response to these agents, further investigation of single agent EGFR-targeted therapy is not warranted.

**Targeted therapy for c-kit**

Overexpression of c-kit was demonstrated in salivary gland carcinomas [15, 22] prompting enthusiasm for the investigation of the c-kit-directed agents imatinib and dasatinib. Three separate studies to date have investigated the use of single agent imatinib and one study has investigated single agent dasatinib. All of the imatinib studies included only patients with c-kit-positive ACC and in total included 43 patients [23–25]. One study by Guigay et al. demonstrated a 13% ORR to imatinib [25] but the other two trials did not show any objective responses [23, 24]. Similarly, in a large phase 2 study, a second generation c-kit inhibitor, dasatinib, demonstrated no objective responses [26].

**Multi-targeted tyrosine kinase inhibitors**

Several multi-targeted tyrosine kinase inhibitors (TKI) have been investigated in advanced salivary malignancies, with the vast majority of the studies being conducted in patients with ACC. The anti-angiogenic TKIs sunitinib and sorafenib have shown overall disappointing results in patients with recurrent or metastatic salivary cancers with sorafenib having the most promise with response rates ranging from (11–22%). No objective responses were seen with sunitinib in patients with ACC,
although five of 14 patients (36 %) did have stable disease and the median OS was 18.7 months; progression within 6 months prior to study therapy was required [27]. Sorafenib has been studied in two trials – one restricted to patients with ACC and one in a mixed population, with non-ACC patients potentially deriving more benefit. Thomson et al. reported an 11 % ORR and a 19.6 month median OS in patients with ACC [28]. Similarly, Locati et al. reported an overall response rate of 16 % with differential response seen in ACC versus non-ACC patients (11 vs 22 %) [29].

Several TKIs have been studied exclusively in patients with ACC; unfortunately, ACC remains an exceptionally treatment-resistant disease. Axitinib - a small molecule inhibitor of vascular endothelial growth factor (VEGF), c-kit, and platelet derived growth factor receptor (PDGFR) - produced three partial responses (9 % ORR) in a single center trial for ACC [30]. Dovitinib - an oral tyrosine-kinase inhibitor that inhibits VEGF and fibroblast growth factor receptors (FGFR) - showed minimal activity in two trials (ORR 3 % and 6 %) and poor tolerability with grade 3/4 asthenia reported in >50 % of patients [31, 32]. Genetic analysis of tumors of patients with ACC showed that a significant number of tumors had mutations involving the FGF-PI3K-AKT pathway [33], however the AKT-inhibitor MK-2206 and the mTOR inhibitor everolimus showed no responses in ACC patients [34, 35]. Similarly, nelfinavir, a proteosome inhibitor, shown to be efficacious in AKT-inhibition, also demonstrated no objective responses in patients with ACC [36]. Even though ACC might have epigenetic dysregulation as a pathogenic mechanism [33], vorinostat - a histone deacetylase inhibitor - failed in an early trial with a reported response rate of 3 % [37].

Although the search for effective targeted therapies for patients with advanced salivary cancer has been elusive, the number of agents being tested continues to increase and recent reports of prolonged disease control in well-designed clinical trials offers some hope for optimism regarding future therapies. At the annual meeting of the American Society of Clinical Oncology (ASCO) in 2016, an unprecedented number of therapeutic trials for recurrent/metastatic salivary gland malignancies were presented. In a phase II study that required documented disease progression prior to enrollment, pazopanib – a multi-kinase inhibitor of VEGFR, PDGFR, and KIT – resulted in prolonged stable disease in both ACC adenoid cystic and non-ACC patients. Although the response

Table 2 Studies with biologic agents

| Author (year) | Regimen | No of patients | Histology | Progression required | ORR | CBR | Median OS (months) |
|---------------|---------|----------------|-----------|----------------------|-----|-----|-------------------|
| Haddad et al. [18] | Trastuzumab | 14 | Ad (7), ACC (2), MEC (3), others (2) | No | 8 % | 8 % | NR |
| Hotte et al. [23] | Imatinib | 16 | ACC (16) | No | 0 % | 56 % | 7 |
| Pfeffer et al. [24] | Imatinib | 10 | ACC (10) | No | 0 % | 20 % | NR |
| Guigay et al. [25] | Imatinib | 17 | ACC (17) | Yes | 13 % | 47 % | NR |
| Agulnik et al. [19] | Lapatinib | 39 | Ad (7), ACC (20), MEC (2), others (11) | Yes | 0 % | 78 % | NR (ACC), 13.8 (non-ACC) |
| Locati et al. [20] | Cetuximab | 30 | ACC (23), MEC (2), others (5) | No | 0 % | 80 % | NR |
| Chau et al. [27] | Sunitinib | 14 | ACC (14) | Yes | 0 % | 85 % | 18.7 |
| Jaspers et al. [44] | Bicalutamide | 10 | SDC (10) | No | 20 % | 50 % | 12 |
| Locati et al. [29] | Sorafenib | 37 | ACC (19), others (18) | No | 16 % | 73 % | NR |
| Thomson et al. [28] | Sorafenib | 23 | ACC (23) | No | 11 % | 79 % | 19.6 |
| Kim et al. [34] | Everolimus | 34 | ACC (34) | Yes | 0 % | 79 % | 23.7 |
| Goncalves et al. [37] | Vorinostat | 30 | ACC (30) | No | 3 % | 87 % | NR |
| Hoover et al. [36] | Nelfinavir | 15 | ACC (15) | Yes | 0 % | 47 % | NR |
| Ho A. et al. [30] | Axitinib | 33 | ACC (33) | Yes | 9 % | 85 % | NR |
| Locati et al. [43] | Bicalutamide + Triptorelin | 17 | SDC (17) | No | 65 % | 88 % | 44 |
| Wong et al. [26] | Dasatinib | 54 | ACC (40), others (14) | Yes | 2 % | 50 % | 14.5 (ACC), NR (non-ACC) |
| Jakob et al. [21] | Gefitinib | 36 | Ad (9), ACC (18), MEC (2), others (6) | No | 0 % | 59 % | 25.9 (ACC), 16 (non-ACC) |
| Dillon et al. [32] | Dovitinib | 35 | ACC (35) | Yes | 6 % | 71 % | 22.1 |
| Ho A. et al. [35] | MK-2206 | 16 | ACC (16) | Yes | 0 % | 93 % | NR |
| Keam et al. [31] | Dovitinib | 32 | ACC (32) | Yes | 3 % | 94 % | NR |

Ad adenocarcinoma, ACC adenoid cystic carcinoma, MEC mucoepidermoid carcinoma, NR not reported
rate was low (two responders – 1 ACC and one non-ACC), the trial met its primary endpoint of 6-month PFS greater than 40 % [38]. Similarly a trial of nintedanib targeting VEGFR1-3, PDGFRα/β, and FGFR1-2 had a disease control rate of 75 % and a 6-month PFS >60 %, although it was not clear if disease progression was required prior to enrollment [39]. Regorafenib, a multi-kinase inhibitor of VEGFR, FGFR, and PDGFR, resulted in prolonged stable disease (>6 months) in ACC patients who had documented progression prior to initiation of therapy [40]. Notably, the microtubular inhibitor eribulin showed a 10 % objective partial response rate in a mixed population of salivary patients, but a striking 69 % of patients had some tumor shrinkage on first tumor assessment and the disease control rate was reported at 90 % [41]. Further exploration of the use of eribulin for salivary cancers appears warranted, and the verdict is still out on the role of multi-kinase inhibitors which perhaps may play a role in select clinical situations or in combination with immunotherapy. Fusion transcripts, such as ETV6-NTRK3 [42], characterize a portion of the salivary gland malignancies and are potential targets for therapy with specific inhibitors (NCT02576431).

## Hormonal therapy

Although no prospective studies have been conducted, it is worthwhile mentioning the data for androgen deprivation in SDC as several reports have emerged in recent years and results have been promising. Retrospective data from a single institution where patients were treated uniformly with bicalutamide and triptorelin showed an impressive ORR of 65 % [43]. In contrast another retrospective study showed an ORR of 20 %. However, the latter study did not treat patients uniformly and most were not treated with a gonadotropin releasing hormone receptor agonist [44]. Recently, case reports have also demonstrated the effectiveness of second-line hormone therapy with abiraterone, a CYP17 inhibitor, after failure of first-line androgen deprivation [45, 46]. Currently, a randomized trial is underway in Europe to study the efficacy of androgen deprivation therapy in androgen receptor-positive salivary cancers (NCT01969578).

## Combination therapy with cytotoxic chemotherapy and biologics

After initial enthusiasm about the possible responses in c-kit overexpressing ACC [15, 22], cisplatin was studied in combination with imatinib. Imatinib was given as an induction regimen at 800 mg daily for 8 weeks followed by the combination of imatinib 400 mg daily with cisplatin 80 mg/m² intravenously every 4 weeks. If patients had stable or responding disease, then imatinib was continued as maintenance therapy. There were only three responses but the median OS was 35 months [47]. As previously mentioned, ACC frequently overexpress EGFR [13, 14]. Hitre et al. studied a regimen similar to the EXTREME regimen [48] in patients with ACC and reported a response rate of 42 % in a cohort of 12 metastatic patients [49]. Finally, a study of the combination of bortezomib, a proteasome inhibitor, and doxorubicin showed minimal response in patients with ACC although the clinical benefit rate for the combination was reported at 58 % [50]. To date, there are no biologic therapies or combinations with chemotherapy that have a clear benefit for patients with advanced salivary cancer.

## Immunotherapy

With the current landscape of cancer therapeutics shifting towards immunotherapy, the obvious question is whether patients with salivary cancer will benefit from these agents. At the present time there is very limited preclinical data for the role of immune checkpoint inhibitors in salivary gland malignancies. A recent study showed that Programmed death Ligand-1 is differentially expressed in various histologies and is a poor prognostic marker for disease-free survival and possibly for overall survival [51]. Despite the lack of robust preclinical data, clinical trials of immune checkpoint inhibitors in salivary cancer are underway. At the 2016 ASCO meeting, preliminary results of the salivary arm of the phase 1b KEYNOTE-028 trial were presented. In the study, patients with advanced salivary cancer (73 % previously treated) received single agent pembrolizumab 10 mg/kg intravenously every 2 weeks for up to 24 months. A total of 26 patients were enrolled with mixed salivary histologies. Three PRs were seen (11.5 %), all in non-ACC patients (two adenocarcinoma, one high-grade serous carcinoma). Twelve patients (46 %) had stable disease and the 6-month PFS was 20.7 % [52]. The role of pembrolizumab monotherapy in salivary cancers continues to be investigated in the phase 2 KEYNOTE-158 basket trial (NCT02628067). Combination immunotherapy or immunotherapy in combination with other agents for salivary cancer is also being investigated in ongoing trials including ipilimumab combined with nivolumab (NCT02834013), oncylucy adenovirus in combination with pembrolizumab (NCT02576431), and histone deacetylase (HDAC) inhibitors in combination with pembrolizumab (NCT02538510). The early signal of efficacy in the KEYNOTE-028 trial opens the door for cautious optimism for immunotherapy in salivary cancers, particular non-ACC histologies.

## Discussion

Salivary gland carcinomas, especially ACC, are notoriously resistant to therapy and no standard of care exists. Platinum-based chemotherapy, if chemotherapy is given,
remains the best option but falls short of being efficacious enough to be considered standard of care. Rarity of these tumors, heterogeneity in behavior, and composition of subjects in each trial make it extremely difficult to systematically study potential new therapies and to compare results across trials and over time. Although in recent years there has been greater success at conducting subtype-specific trials, at least for ACC. Of note, the number of trials published for salivary cancer has steadily climbed from 0 to 1 per year in the time period 2008–2010 to 4–6 per year in the period from 2014 to 2015, a remarkable feat given the rarity of salivary cancer, and a critical step in finding novel therapeutic approaches for this disease.

As with many solid tumors, there is often a discrepancy between preclinical data, possible therapeutic mechanisms, and the results of clinical trials. We have yet to find effective targeted therapy that is widely applicable to salivary gland carcinomas. Multiple reports had demonstrated the expression of several potential targets in salivary cancers including c-kit, EGFR, and HER-2, thus prompting a new generation of trials [14–16, 22]. Despite strong scientific rationale, imatinib and dasatinib failed to demonstrate clinical benefit. One confounding factor was the heterogenous criteria for c-kit staining, and the lack of ability to correlate the degree of positive of c-kit staining with response [53]. Similarly, there is no data to determine whether the response rates are correlated to any c-kit mutations. However, c-kit mutations are not very common in salivary gland carcinoma [15]. Despite the fact that the genomic landscape of ACC is known [33], there is not a clear direction forward for salivary cancers as a whole. Individualized medicine may offer the most benefit for patients with the ability to test for driver mutations in individual patients and to tailor therapy to the patient’s tumor, from both a clinical and molecular standpoint.

Despite the overall modest results of new trials of chemotherapeutic and biologic agents, there are some notable glimmers of hope on the horizon for the treatment of advanced salivary cancers. Adenocarcinoma of the salivary gland appears to be more treatment responsive with a higher likelihood of benefit from cytotoxic chemotherapy and a preliminary signal of responsiveness to immune checkpoint inhibitors [8, 9, 11, 49]. The microtubular inhibitor eribulin deserves further evaluation given the promising disease control rate and initial tumor shrinkage that was reported in a mixed population of salivary patients; further defining which subtypes benefit the most from this agent would be helpful. The use of hormone therapy and anti-HER2 therapy for salivary duct carcinoma or AR+/HER2+ adenocarcinoma is a treatment approach that should continue to be refined and investigated. The head and neck medical oncology community will be eagerly awaiting the results of future trials of immunotherapy-based treatments that hopefully will move the practice forward and break through the therapeutic plateau that has likely been reached for cytotoxic agents; further refinement of our use of targeted agents should continue. Given the clinical rarity and nuances of each salivary cancer subtype and the changing academic landscape with a steadily increasing number of therapeutic options and clinical trials, management by an experienced head and neck medical oncologist at a tertiary referral center or academic institution is preferred if possible. Patients with advanced salivary cancers should have the opportunity to participate in salivary cancer-specific trials and/or to have access to genomic testing to open the door for appropriate phase 1 clinical trials or individualized targeted treatment with the off-label use of available agents. An experienced oncologist who sees a significant number of patients with advanced salivary cancer will be able to appreciate the clinical and biologic variability even within a certain subtype of salivary cancer, and to avoid a “once size fits all” approach which has not worked for this patient population.

From a practical standpoint, how do we typically approach our patients with advanced salivary malignancies? With the lack of high quality evidence to guide treatment and the heterogeneity of the tumors, a standard of care treatment approach to patients with recurrent or metastatic salivary is difficult to devise but with the available data we generally follow the approach outlined in Fig. 1. If the patient has a low disease burden with isolated or oligometastatic disease that is amenable to local therapies, then we typically recommend local therapy with stereotactic body radiation therapy or cryoablation. If a patient does not have an adequate performance status, then best supportive care is appropriate. In a fit patient the need to treat is balanced with the risks of systemic therapy. In a patient with slow growing, indolent disease such as classic ACC, we prefer observation. If therapy is required due to disease burden, symptoms, or an aggressive clinical course, or if the patient desires treatment (after discussion of risks and benefits), we consider systemic treatment with either standard chemotherapy, targeted therapy, or a clinical trial (preferred). In patients for whom chemotherapy is indicated we most commonly would use a platinum doublet. We routinely perform genomic testing for all patients with recurrent or metastatic salivary cancer to see if targeted therapy can be used either off-label or through a phase 1 clinical trial. For patients with adenocarcinoma and SDC we routinely perform androgen receptor staining and HER-2 testing. If they are strongly positive for androgen receptor then we prefer treating them with combined androgen–deprivation therapy with bicalutamide and leuprolide, or leuprolide alone, or with anti-HER-2
therapy if HER-2 is positive (immunohistochemistry 3+ staining). Those patients with an initial response to androgen deprivation therapy who subsequently progress will often be treated with second-line hormone therapy with abiraterone.

**Conclusion**

It has been challenging to find effective therapies for salivary cancers but it is imperative that we continue to pursue research studies. Laurie and colleagues have put forth some recommendations for testing therapies in rare tumors such as salivary gland malignancies to increase coordination, avoid duplication, and increase accrual to clinical trials [54]. The studies reviewed here provide no standard of care for the treatment of salivary gland malignancies, but suggest a future landscape of heterogenous and individualized treatment for patients with salivary cancer. The advent of immunotherapy and the increase in clinical trials in recent years for salivary cancer offer hope for new therapeutic opportunities and research collaboration.

**Funding**

None.

**Availability of data and material**

No raw data used.

**Authors’ contributions**

AVC carried out the literature search and drafted the manuscript. All authors read, edited and approved the final manuscript.

**Competing interests**

The authors declare that they have no competing interests.

---

**Consent for publication**

Not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Received:** 22 February 2016 **Accepted:** 9 August 2016
**Published online:** 01 September 2016

**References**

1. Spiro RH. Management of malignant tumors of the salivary glands. Oncology (Williston Park). 1998;12(5):671–80. discussion 683.
2. Barnes L, Everson JW, Reichart P, Sidransky D, editors. World Health Organization Classification of Tumors. Lyon: IARC Press; 2005.
3. Laurie SA, Licitra L. Systemic therapy in the palliative management of advanced salivary gland cancers. J Clin Oncol. 2006;24(17):2673–8.
4. Licitra L, Cavina R, Grandi C, Palma SD, Guzzo M, Demicheli R, Molinari R. Cisplatin, doxorubicin and cyclophosphamide in advanced salivary gland carcinoma. A phase II trial of 22 patients. Ann Oncol. 1996;7(6):640–2.
5. Dreyfuss AI, Clark JR, Fallon BG, Posner MR, Norris Jr CM, Miller D. Cyclophosphamide, doxorubicin, and cisplatin combination chemotherapy for advanced carcinomas of salivary gland origin. Cancer. 1987;60(12):2869–72.
6. Airoldi M, Pedani F, Succo G, Gabriele AM, Ragona R, Marchionatti S, Bumma C. Phase II randomized trial comparing vinorelbine versus vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies. Cancer. 2001;91(3):541–7.
7. Gedlicka C, Schull B, Formanek M, Komfehl J, Burian M, Nкриer B, Seiber E, Scheithauer W, Kornek GV. Mitoxantrone and cisplatin in recurrent and/or metastatic salivary gland malignancies. Anticancer Drugs. 2002;13(5):491–495.
8. Laurie SA, Siu LL, Winguest E, Maksymik A, Harnett EL, Walsh W, Tu D, Parulekar WR. A phase II study of platinum and gemcitabine in patients with advanced salivary gland cancer: a final report of the NCIC Clinical Trials Group. Cancer. 2010;116(2):362–8.
9. Airoldi M, Garzaro M, Pedani F, Ostellino O, Succo G, Riva G, Sensini M, Nagel N, Bellini E, Raimondo L, et al. Cisplatin + Vinorelbine Treatment of Recurrent or Metastatic Salivary Gland Malignancies (RMSGM): A Final Report on 60 Cases. Am J Clin Oncol. 2014. PMID: 25089531.
10. Ross PJ, Teoh EM, A’Hern RP, Rhys-Evans PH, Harrington KJ, Nutting CM, Gore ME, Epirubicin, cisplatin and protracted venous infusion 5-Fluorouracil chemotherapy for advanced salivary adenoid cystic carcinoma. Clin Oncol (R Coll Radiol). 2009;21(4):311–4.
11. Gilbert J, Li Y, Pinto HA, Jennings T, Kies MS, Silverman P, Forastiere AA. Phase II trial of taxol in salivary gland malignancies (E1394); a trial of the Eastern Cooperative Oncology Group. Head Neck. 2006;28(3):197–204.
12. van Herpen CM, Locati LD, Butler J, Thomas J, Bogaerts J, Lacombe D, de Mulder P, Awada A, Licitra L, Bernier J, et al. Phase II study on gemcitabine in recurrent and/or metastatic adenoid cystic carcinoma of the head and neck (EORTC 24982). Eur J Cancer. 2008;44(17):2542–5.
13. Gibbons MD, Manne U, Carroll WR, Peters GE, Weiss HL, Grizzle WE. Molecular differences in mucoepidermoid carcinoma and adenoid cystic carcinoma of the major salivary glands. Laryngoscope. 2001;111(18):1373–8.
14. Vered M, Braunstein E, Buchner A. Immunohistochemical study of epidermal growth factor receptor in adenoid cystic carcinoma of salivary gland origin. Head Neck. 2002;24(7):632–6.
15. Holst VA, Marshall CE, Moskaluk CA, Frierson Jr HF. KIT protein expression and analysis of c-kit gene mutation in adenoid cystic carcinoma. Mod Pathol. 1999;12(10):956–60.
16. Giannoni C, el-Naggar AK, Ordonez NG, Tu ZN, Austin J, Luna MA, Batsakis JG. c-erbB-2/Her-2neu oncogene and Ki-67 analysis in the assessment of palatal salivary gland neoplasms. Oncology. Head Neck Surg. 1995;11(2):391–8.
17. Limaye SA, Posner MR, Krane JF, Fonfria M, Lorch JH, Dillon DA, Shreenivas AV, Tishler R, Haddad R. Trastuzumab for the treatment of ductal adenocarcinoma of the salivary glands. Ann Oncol. 2013;18(3):394–300.
18. Haddad R, Colevas AD, Kranje JF, Cooper D, Glisson B, Amrein PC, Weeks L, Costello R, Posner M. Herceptin in patients with advanced or metastatic salivary gland malignancies. A phase II study. Oncol. 2003;39(7):724–728.
19. Aguilin M, Cohen EW, Cohen RB, Chen EX, Vokes EE, Hotte SJ, Winquist E, Laurie S, Hayes DN, Dancey JE, et al. Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands. J Clin Oncol. 2007;25(25):3978–84.
20. Locati LD, Bossi P, Perrone F, Potesan P, Crippa F, Manieri L, Castlei P, Orsenigo M, Losa M, Bergamini C, et al. Cetuximab in recurrent and/or metastatic salivary gland carcinomas: a phase II study. Oral Oncol. 2009;45(7):574–8.
21. Jakob JA, Kies MS, Glisson BS, Kupferman ME, Liu DD, Lee JJ, el-Naggar AK, Gonzalez-Angulo AM, Blumenschein Jr GR. Phase II study of gefitinib in patients with recurrent and/or metastatic salivary gland carcinomas. Cancer. 2000;154(1):107–11.
22. Hotte SJ, Winquist EW, Lamont E, Mackenzie M, Vokes E, Chen EX, Brown S, Pond GR, Mugo A, Siu LL. Imatinib mesylate in patients with adenocystic cancers of the salivary glands expressing c-kit: a Princess Margaret Hospital phase II consortium study. J Clin Oncol. 2005;23(3):585–90.
23. Pfeifer MR, Talmi Y, Catane R, Symon Z, Yosepovich A, Levit M. A phase II study of Imatinib for advanced adenoid cystic carcinoma of the head and neck salivary glands. Oral Oncol. 2007;43(1):133–6.
24. Guigay JM, Bidault F, Temam S, Janot F, Raymond E, Faivre S. Antitumor activity of imatinib in progressive, highly expressing Kit adenoid cystic carcinoma of the salivary glands: A phase II study. ASCO Meeting Abstracts. 2007;25(18_suppl):6086.
25. Wong SJ, Karrison T, Hayes DN, Kies MS, Cullen KJ, Tanyeyanont T, Agris A, Takebe N, Lim D, Saba NF, et al. Phase II trial of dasatinib for recurrent or metastatic c-kit-expressing adenoid cystic carcinoma and for nonadenoid cystic malignant salivary tumors. Ann Oncol. 2016;27(2):318–323.
26. Chau NG, Hotte SJ, Chen EX, Chin SF, Turner S, Wang L, Siu LL. A phase II study of sunitinib in recurrent and/or metastatic adenoid cystic carcinoma (ACC) of the salivary glands: current progress and challenges in molecularly targeted agents in ACC. Ann Oncol. 2012;23(6):1562–70.
27. Thomson DJ, Silva P, Denton K, Bonington S, Mak SK, Swindell R, Homer J, Sykes AJ, Lee LW, Yap BK, et al. Phase II trial of sorafenib in advanced salivary adenoid cystic carcinoma of the head and neck. Head Neck. 2015;37(2):182–7.
28. Locati LD, Bossi P, Civiello EM, Perrone F, Bergamini C, Cortelazzi B, Quattrocchi P, Imbimbo M, Mirabile A, Granata R, et al. Sorafenib in recurrent and/or metastatic salivary gland carcinomas (RMSGC): An investigator-initiated phase II trial (NCT01703455). ASCO Meeting Abstracts. 2013;33(15_suppl):6090.
29. Ho AL, Sherman EJ, Fury MG, Baxi SS, Haque S, Sima CS, Antonescu CR, Katabi N, Pfizer DG. Phase II study of axitinib in patients with progressive, recurrent/metastatic adenoid cystic carcinoma. ASCO Meeting Abstracts. 2013;33(15_suppl):6093.
51. Mukaigawa T, Hayashi R, Hashimoto K, Uegumori T, Hato N, Fujii S. Programmed death ligand-1 expression is associated with poor disease free survival in salivary gland carcinomas. J Surg Oncol. 2016;114(1):36–43.

52. Cohen RB, Delord J-P, Doi T, Piha-Paul SA, Liu SV, Gilbert J, Algazi AP, Cresta S, Hong R-L, Le Tourneau C, et al. Preliminary results for the advanced salivary gland carcinoma cohort of the phase 1b KEYNOTE-028 study of pembrolizumab. ASCO Meeting Abstracts. 2016;34(15_suppl):6017.

53. Faivre S, Raymond E, Casiraghi O, Temam S, Berthaud P. Imatinib mesylate can induce objective response in progressing, highly expressing KIT adenoid cystic carcinoma of the salivary glands. J Clin Oncol. 2005;23(25):6271–3. author reply 6273–6274.

54. Laurie SA, Ho AL, Fury MG, Sherman E, Pfister DG. Systemic therapy in the management of metastatic or locally recurrent adenoid cystic carcinoma of the salivary glands: a systematic review. Lancet Oncol. 2011;12(8):815–24.