Systemic therapy for salivary gland malignancy: current status and future perspectives

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Running head: Systemic therapy for salivary gland malignancy

Abstract

Salivary gland malignancies (SGMs) are rare neoplasms which have a broad histological spectrum and a variety of biologic behaviors. SGMs are known as chemo-resistant tumors, which renders optimal treatment challenging. This review summarizes the role of systemic therapy for SGMs. To date, the advantage of adding concurrent chemotherapy has remained undefined for both post-operative and inoperable locally advanced SGM patients undergoing radiotherapy. For recurrent/metastatic disease, local and/or systemic treatment options should be discussed in a multidisciplinary setting with consideration to both patient needs and tumor factors. For symptomatic patients or those who may compromise organ function, palliative systemic therapy can be a reasonable option based on the results of phase II studies. Platinum-combination regimens as first-line therapy have been widely accepted. Personalized therapies have become established options, particularly for androgen receptor (AR)-positive, HER2-positive, and *NTRK* fusion-positive SGMs (ie. AR and HER2 in salivary duct carcinoma, and *NTRK3* in secretory carcinoma). For patients with adenoid cystic carcinoma, multi-targeted tyrosine kinase inhibitors have also been developed. Anti-PD1 checkpoint inhibitors have shown limited activity to date. Investigation of active systemic treatments for SGM remains a significant unmet need. Future directions might include a more comprehensive genomic screening approach (usually next-generation sequencing-

based) and combination strategies using immune checkpoint inhibitors. These are rare malignancies which require ongoing effort in the conduct of high-quality clinical trials.

Key words: salivary gland malignancy, chemotherapy, personalized therapy, immunotherapy

Introduction

Salivary gland malignancies (SGMs) are rare neoplasms that account for fewer than 0.5% of all malignancies and about 5% of cancers of the head and neck (1). SGMs consist of up to 20 distinct histopathologic entities (2), and this histological heterogeneity may contribute to diversity in clinical behavior and prognosis. Due to this rarity and limited number of animal models (3), few clinical trial data are available to help guide therapy especially histotype-specific approach. Furthermore, SGMs are known as chemo-resistant tumors that are challenging to treat optimally. A recent ASCO guideline provided management recommendations for SGMs based on published literature and an expert panel consensus (4). The present review incorporates the topics specifically covered in the ASCO guideline, namely cytotoxic chemotherapy, personalized therapy, and immune check point inhibitors, and includes additional evidence presented at international conferences which aimed to summarize optimal management approaches and therapeutic outcomes for these rare diseases. Future directions might include a more comprehensive genomic screening approach and combination strategies using immune checkpoint inhibitors. The epidemiology, risk factors, pathology, and clinical features of SGMs are reviewed elsewhere (3,5-7).

Postoperative radiotherapy with or without concomitant chemotherapy

Data supporting the role of postoperative radiotherapy in patients with high-risk features such as high-grade histology, advanced stage, nodal status and/or positive surgical margins are available (8-11); nevertheless, the benefit of adding concurrent chemotherapy remains controversial. This is because survival outcomes in patients with SGM candidates for postoperative radiotherapy have not been compared in randomized trials between those with or without concomitant chemotherapy. Of the eight most relevant retrospective studies (n ≥100 of any histology, or n≥ 50 of a specific histology), only two showed an advantage following the addition of chemotherapy to postoperative radiotherapy (10-17) [Table 1]: the first showed an improvement in overall survival (OS) for squamous cell carcinoma (11) while the second observed an advantage in local control for adenoid cystic carcinoma (AdCC) (12). These inconsistent findings included a degree of selection bias, regarding not only oncological features but also patient characteristics (ie. age, performance status, and comorbidity). Against this background, the latest ASCO guideline did not recommend the routine use of adjuvant concurrent chemoradiotherapy in patients with SGMs outside of a clinical trial (4).

At least three prospective studies to evaluate the efficacy and safety of concurrent chemotherapy in this adjuvant setting are now ongoing (NCT02776163, NCT01220583, NCT02998385) [Table 2]. Their eligibility criteria are similar but not identical. These studies should identify the most relevant high-risk factors, as in the case of head and neck squamous cell carcinoma (18).

Adjuvant androgen deprivation therapy (ADT) and HER2–targeted therapies

No randomized trial has compared survival outcomes in patients with SGMs expressing androgen receptor (AR) and/or HER2 between those with or without adjuvant systemic therapy, and only retrospective data are available (19-21) [Table 3]. Although results are promising, further prospective evaluation of efficacy and safety is required, along with efforts to identify the optimal agent(s), duration, and most relevant high-risk factors of use in routine practice.

At least one prospective study aimed at addressing these issues is now ongoing (NCT04620187). The aim of this study is to evaluate efficacy and safety of postoperative radiotherapy with concurrent trastuzumab emtansine (T-DM1).

Concurrent systemic therapy for inoperable locally advanced disease

No randomized trial or prospective study have compared survival outcomes in patients with inoperable SGM candidates receiving definitive radiotherapy between those with or without concomitant chemotherapy. Only case series have been reported in patients with locally advanced SGMs or AdCC of the head and neck (22-26) [Table 4]. It is noteworthy that cisplatin-based chemoradiotherapy is associated with some long-term local control of unresected AdCC, although this promising result may simply be due to full-dose radiotherapy or proton therapy. Because the

benefit of adding concurrent chemotherapy is unclear, the ASCO Guideline does not recommend the routine use of concurrent chemoradiotherapy in patients with inoperable SGMs (4).

Initiating systemic therapy for recurrent/metastatic disease

Palliative systemic therapy is a key part of treatment for recurrent/metastatic SGMs. Nevertheless, some patients survive for an extended period (> 10 years), particularly in the setting of low-grade tumors with indolent biology (ie. AdCC). In this context, for patients with limited metastases (ie. ≤ 5 metastases (27)), palliative local therapy such as metastasectomy or stereotactic body radiation therapy may be a treatment option, with the aim of delaying local disease progression (28-30).

The ASCO Guideline recommended that initiation of systemic therapy should be considered under the following conditions: (i) metastatic tumors are symptomatic and not amenable to palliative local therapy, (ii) growth has the potential to compromise organ function, or (iii) lesions have grown more than 20% in the preceding 6 months (4). Accordingly, local and/or systemic treatment options need to be discussed in a multidisciplinary setting with consideration to both patient context and tumor factors.

Cytotoxic chemotherapy for recurrent/metastatic disease

In prospective trials of cytotoxic regimens for SGMs, patients appear to show clinically relevant objective responses to cytotoxic chemotherapy [Table 5].

In early phase II studies, single-agent cytotoxic agents provided modest efficacy with objective response rates (ORRs) of 0%-20% (31-36). Not surprisingly, objective responses in patients with AdCC were disappointing: among AdCC patients who initiated therapy with paclitaxel or gemcitabine, for examples, no objective responses were observed (34,35).

To date, platinum combination therapy has been regarded as the most promising regimen. In a randomized phase II trial, for example, Airoldi and colleagues reported that the combination of cisplatin plus vinorelbine was more active than vinorelbine alone (36), showing a good risk/benefit balance with ORRs of 33%-44% and median overall survival (OS) of 10-16.9 months (36-38). CAP (cyclophosphamide, doxorubicin, cisplatin) has also been reported as an active regimen in SGMs. The reported ORR from multiple studies (39-44) was 46% (43 of 92), although in the largest phase II trial of 22 patients treated with CAP, Licitra and colleagues reported that only 6 patients achieved a partial response, giving an ORR of 27% (39). In addition, platinum plus taxane combination therapy can be a good treatment choice (45-48): indeed, the reference arm of an ongoing randomized phase II study comparing ADT to cytotoxic regimens in recurrent/metastatic AR-positive SGMs was cisplatin plus docetaxel or carboplatin plus paclitaxel (NCT01969578).

144 Thus, against a lack of high-level evidence for a survival benefit over best supportive care,
145 platinum combination therapy has become the most common option for systemic therapy for
146 recurrent/metastatic SGM patients with progressive or symptomatic disease. No consensus has yet
147 been reached on what the standard regimen should be in this setting (49).
148
149 **Personalized therapy for recurrent/metastatic disease**
150 A number of studies demonstrated that selected targetable oncogenic drivers have an
151 exceptionally high prevalence in specific histologic types (ie. *HER2* amplification in salivary duct
152 carcinoma [SDC] or adenocarcinoma, not otherwise specified [ANOS] (50), and *ETV6-NTRK3*
153 translocation in secretory carcinoma (51)). AR expression is also notable in SDC and ANOS (50).
154 Targeted therapy for these patients should include confirmatory target-specific testing. In addition,
155 these patients may be offered personalized therapy in place of cytotoxic chemotherapy, given the
156 high efficacy and favorable toxicity profile of this therapy. Evidence for ADT, HER-2 targeted
157 therapy, and *NTRK* inhibitors will be described separately.
158 Non-targetable molecular alterations have also been documented. For example, *KIT*, *EGFR*,
159 *AKT/mTOR* pass-way, or c-MET inhibitors for AdCC showed disappointing efficacy, with ORRs of
160 0%-7% in a number of phase II studies (52-62) [Table 6].

On the other hand, several phase II studies have demonstrated the activity of multi-targeted tyrosine kinase inhibitors (mTKIs) in AdCC including lenvatinib (63,64), sorafenib (65,66), and axitinib (67-69) [Table 6], and the ASCO Guideline recommended that these agents may accordingly be offered for AdCC patients who are candidates for the initiation of systemic therapy (4). In contrast, sunitinib, nintedanib, pazopanib, and regorafenib failed to demonstrate their efficacy in both AdCC and non-AdCC patients (70-73). The reason for these inconsistent results has not been fully clarified.

Androgen deprivation therapy (ADT) for recurrent/metastatic disease

For patients with AR-positive SGMs (ie. SDC and ANOS), ADT can be provided in the first- or subsequent-line setting [Table 7]. In a nationwide case series of bicalutamide plus or minus luteinizing hormone-releasing hormone (LHRH) analog involving 35 patients in the Netherlands (74), the ADT-treated patients had a significantly better OS than those receiving best supportive care in a Cox regression model (hazard ratio 0.53). A single-arm phase II trial of first-line bicalutamide plus leuprorelin involving 36 patients with AR-positive SGMs reported an ORR of 42% and median progression-free survival (PFS) of 8.8 months (75). The reported ORR with a first-line AR antagonist (enzalutamide or bicalutamide) and/or LHRH analog based on multiple studies (74-79) was 33% (30 of 90). In addition, second-line AR antagonist (enzalutamide or abiraterone)

plus/minus LHRH analog achieved clinically meaningful disease control rates of 63%-67% and median PFS of 3.7-5.5 months in single-arm phase II studies (80,81).

HER2-targeted therapy for recurrent/metastatic disease

For patients with HER2-positive SGMs (ie. SDC and ANOS), HER2-targeted therapies can be administered in the first- or subsequent-line setting [Table 7]. Two single-arm phase II trials of first- or subsequent-line trastuzumab plus docetaxel reported ORRs of 60%-70% and median PFS of 8.5-8.9 months (82,83). Similarly, a phase IIa basket trial of first- or subsequent-line trastuzumab plus pertuzumab demonstrated an ORR of 60% and median PFS of 8.6 months (84). These combination therapies had higher ORRs than those of single-agent cytotoxic agents or trastuzumab monotherapy (0-20%) (31-35,85). In addition, HER2-tageting antibody-drug conjugates such as T-DM1 and trastuzumab deruxtecan (T-DXd) showed clinically meaningful efficacies in multiple basket trials (86,87).

A prospective Japanese study to assess the efficacy and safety of T-DXd both in HER2-positive and in HER2-low SGMs is currently under preparation.

NTRK inhibitors for recurrent/metastatic secretory carcinomas

196 Secretory carcinoma represents 5% of SMGs with morphological overlap with acinic cell
197 carcinoma, mucoepidermoid carcinoma, and ANOS (88,89). As a critical difference, secretory
198 carcinoma characteristically harbors *NTRK* gene fusion (95%-98%, *ETV6-NTRK3* translocation (2))
199 and are excellent candidates for NTRK inhibitor therapy in the first- or subsequent-line setting
200 [Table 7]. Two pooled analyses consisting of phase I/II trials of entrectinib and larotectinib revealed
201 ORRs of 86%-90% with a long duration of response (90,91).
202
203 **Roles of comprehensive genomic screening in SGMs**
204 For patients with a low prevalence of targetable molecular alterations and an unknown driver
205 mutation status, a more comprehensive genomic screening approach (usually next-generation
206 sequencing-based) may be useful. This platform may provide information about unanticipated
207 druggable targets such as ALK (92), tumor mutational burden (93), or microsatellite instability (94).
208 At least one prospective tumor agonistic study which includes SGMs is evaluating genomic
209 matched therapy (EGFR, HER2, FGFR, c-kit, AR, NOTCH, MEK, PI3K; NCT02069730), and will
210 likely identify novel treatment seeds.
211
212 **Anti-PD1 checkpoint inhibitors for recurrent/metastatic disease**

Several prospective and retrospective experiences with anti-PD1 checkpoint inhibitors in SGMs have been reported (95-99) [Table 8]. Considerable selection bias was present (heterogenous histologies and variations in study design and eligibility), and findings are currently unsatisfactory. Combination immunotherapy has also been investigated (100-102) [Table 8]. Although each combination strategy has a basic rationale (103), the effectiveness for SGMs is unfortunately modest, and no definitive biomarkers have been detected.

Featured ongoing clinical trials for recurrent/metastatic disease

As listed in Table 9, several phase II trials for recurrent/metastatic SGM are underway, which include personalized therapy and combination immunotherapy with a variety of partners. Further, a number of tumor agnostic clinical trials are now ongoing (ie. T-DXd for unresectable/metastatic solid tumors harboring HER2 activating mutation; NCT04639219). Their findings will aid in optimizing agent(s) and sequencing, and will assist the development of novel treatment options. The next breakthrough will require patience and consistent effort.

Conclusions

Because of the rarity of SGM, few adequate clinical trials are available with which to define an optimal systemic approach. Further investigation of active systemic treatments for SGMs is still

required. Additional efforts to conduct high-quality clinical trials (ie. combination immunotherapy) for these rare malignancies are warranted. These trials should be accompanied by translational research which includes a next-generation-sequencing-based approach.

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Table 1. Major retrospective studies of postoperative concurrent chemoradiotherapy for resected salivary gland malignancies

Treatment	N	Histology	DFS or PFS	OS	Interpretation	Adverse features
CRT (vs RT) (10)	3141	Any	NA	47.3% (5Y) HR 1.03	Negative	Histology, tumor grade, positive margins, or pathologic node involvement
CRT (vs RT) (12)	140	Any	42.1% vs 73.8% (3Y) HR 0.78 (0.40-1.55)	52.2% vs 78.1% (3Y)	Negative	Age, T classification, N classification, tumor grade, or extra nodal extension
CRT (vs RT) (14)	2210	Any	NA	38.5% vs 54.2% (5Y) aHR 1.22 (1.03-1.44)	Negative	T3-4, N1-3, or positive margins
CRT (vs RT) (15)	148	SDC	NA	40.9% vs 38.8% (5Y)	Negative	NA
CRT (16)	128	Any	61.2% (5Y)	73.7% (5Y)	Negative	T3-4, N1-3, positive margins, and extra nodal extension
CRT (vs RT) (17)	741 (≥66 y)	Any	NA	24.0M vs 41.0M aHR 1.39 (1.07-1.79)	Negative	Age, number of positive nodes, histology, or IMRT
CRT (vs RT) (11)	1052	SqCC	NA	58.4% vs 45.0% (5Y)	Positive	NA
CRT (vs RT) (12)	91	AdCC	96% vs 96% (5Y) 88% vs 78% (8Y)	(No statistically significant difference)	Positive	Stage III/IV, positive margins, and perineural invasion

AdCC, adenoid cystic carcinoma; aHR, adjusted hazard ratio; CRT, chemoradiotherapy; IMRT, intensity modulated radiation therapy; NA, not available; SDC, salivary duct carcinoma; SqCC, squamous cell carcinoma

Table 2. Ongoing prospective studies of postoperative concurrent chemoradiotherapy

Treatment	Study design	N	Primary endpoint	Histology	Other key eligibility
Cisplatn/docetaxel +RT (NCT02776163)	Phase II	53	Disease-free survival	Int-grade, or high-grade	T3-4 or N1-3 or T1-2 N0 with inadequate surgical margin (≤5mm)
Cisplatin+RT vs RT-alone (NCT01220583)	Phase II/III	252	Progression-free survival	Int-grade ANOS. int-grade MEC, high-grade acinic cell carcinoma, or high-grade AdCC	T3-4 or N1-3 or T1-2 N0 with inadequate surgical margin (≤1mm)
Cisplatin+RT vs RT-alone (NCT02998385)	Phase III	260*	Progression-free survival	AdCC, high-grade ANOS, int/high-grade MEC, SDC, etc	T3-4 or N1-3 or T1-2 N0 with inadequate surgical margin (<5mm)

*Including unresectable or not operable tumors

AdCC, adenoid cystic carcinoma; ANOS adenocarcinoma, not otherwise specified; MEC mucoepidermoid carcinoma; RT, radiotherapy; SDC, salivary duct carcinoma

Table 3. Retrospective studies of adjuvant androgen deprivation therapy and HER2–targeted therapies for resected salivary gland malignancies

Treatment	N	Histology	Target	mDFS (M)	mOS (M)
Bicalutamide and/or LHRHa (19)	22	SDC	AR	33 (vs 21) HR 0.14 (0.03-0.75)	- HR 0.06 (0.01-0.76)
Carboplatin/paclitaxel /trastuzumab (20)	8	SDC	HER2	62% (2Y)	NA
Carboplatin/paclitaxel /trastuzumab (21)	9	SDC	HER2	117 (vs 9)	74 (vs 43)

HR, hazard ratio; LHRHa, luteinizing hormone-releasing hormone analog; mDFS, median disease-free survival; mOS median overall survival; NA, not available; SDC, salivary duct carcinoma; T-DM1, trastuzumab emtansine

Table 4. Retrospective studies of definitive concurrent chemoradiotherapy for locally advanced salivary gland malignancies

Treatment	N	Histology	ORR	LC	PFS	OS
Platinum-based (22)	7	1 AdCC (14%)	NA	4 failures	NA	NA
Cyclophosphamide/pirarubicin/cisplatin (23)	17	4 AdCC (24%)	76% (CR, 23%)	5 failures	NA	70% (5Y)
Cisplatin (24)	9	AdCC*	44% (CR, 44%)	1 failure	NA	NA
Carboplatin/paclitaxel (25)	5	AdCC*	100%	100% (3Y)	NA	20-43M
Platinum (26)	16	AdCC*	88% (CR, 44%)	61% (5Y)	39% (5Y)	87% (5Y)

*AdCC of the head and neck

AdCC, adenoid cystic carcinoma; CR, complete response; LC, local control; NA, not available; OS overall survival; ORR, objective response rate; PFS, progression-free survival; SGM, salivary gland malignancy

Table 5. Largest phase II trials of respective cytotoxic regimens for recurrent/metastatic salivary gland malignancies

Treatment	N	Histology	ORR (AdCC, %)	ORR (non-AdCC, %)	mPFS (M)	mOS (M)
Cisplatin (31)	25	13 AdCC (52%)	15	17	NA	14
Epibubicin (32)	20	AdCC only	10	-	4	15.5
Mitoxantrone (33)	18	AdCC only	6	-	NA	19
Paclitaxel (34)	45	14 AdCC (31%)	0	26	4	12.5
Gemcitabine (35)	21	AdCC only	0	-	NA	NA
Vinorelbine (36)	20	13 AdCC (65%)	15	29	NA	8.5
Cisplatin/vinorelbine (38)	40	19 AdCC (48%)	32	38	6.3	16.9
Cyclophosphamide/doxorubicin/ cisplatin (39)	22	12 AdCC (55%)	25	30	NA	21
Carboplatin/paclitaxel (45)	14	10 AdCC (71%)	20	0	NA	12.5
Cisplatin/docetaxel (46)	11	4 AdCC (36%)	50	57	6.6	18.8
Cisplatin/fluorouracil (104)	14	AdCC only	0	-	9	12
Cyclophosphamide/doxorubicin/ cisplatin/fluorouracil (105)	17	7 AdCC (44%)	43	50	NA	16.6
Platinum/gemcitabine (106)	33	10 AdCC (30%)	20	26	NA	13.8

AdCC, adenoid cystic carcinoma; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; ORR, objective response rate; SDC, salivary duct carcinoma

Table 6. Phase II trials of targeted therapies for recurrent/metastatic salivary gland malignancies (except AR, HER2, and NTRK)

Treatment	N	Histology	Target	ORR (AdCC, %)	ORR (non-AdCC, %)
Imatinib (52-54)	44	AdCC only	KIT	5	-
Dasatinib (55)	54	40 AdCC (74%)	KIT	3	0
Lapatinib (56)	36	19 AdCC (53%)	EGFR/HER2	0	0
Gefitinib (57)	36	18 AdCC (50%)	EGFR	0	0
Cetuximab (58)	30	23 AdCC (77%)	EGFR	0	0
Everolimus (59)	34	AdCC only	mTOR	0	-
Nelfinavir (60)	15	AdCC only	AKT	0	-
MK-2206 (61)	14	AdCC only	AKT	0	-
Cabozantinib (62)	21	15 AdCC (71%)	c-MET/VEGFR	7	17
Bortezomib (107)	24	AdCC only	NF-κB	0	-
Dovitinib (108,109)	66	AdCC only	FGFR	5	-
Vorinostat (110)	30	AdCC only	HDAC	7	-
Tipifarnib (111)	12	1 AdCC (8%)	HRAS	100 (1/1)	0
All-trans retinoic acid (112)	18	AdCC only	MYB	0	-
Lenvatinb (63,64)	58	AdCC only	VEGFR/FGFR/PDGFR /RET/KIT	14	-
Sorafenib (65,66)	56	38 AdCC (68%)	BRAF/VEGFR/PDRFR	11	22
Axitinib (67-69)	89	69 AdCC (78%)	VEGFR	7	5
Sunitinib (70)	14	AdCC only	VEGFR/PDGFR	0	-
Nintedanib (71)	20	13 AdCC (65%)	VEGFR/PDGFR/FGFR	0	0
Pazopanib (72)	69	49 AdCC (71%)	VEGFR/PFGFR/KIT	2	6
Regorafenib (73)	38	AdCC only	VEGFR/RET/PDGFR	0	-

AdCC, adenoid cystic carcinoma; ANOS, adenocarcinoma, not otherwise specified; ORR, objective response rate

Table 7. Prospective studies of targeted therapies for recurrent/metastatic salivary gland malignancies (AR, HER2, and NTRK)

Treatment	Study design	N	Histology	Target	ORR (%)	mPFS (M)	mOS (M)
Bicalutamide/leuprorelin (75)	Phase II	36	SDC/ANOS	AR	42	8.8	30.5
Enzalutamide (80)	Phase II	45	SDC	AR	15	5.5	NR
Abiraterone/LHRHa (81)	Phase II	24	SDC/ANOS	AR	21	3.7	22.5
Trastuzumab (85)	Phase II	13	Any	HER2	NA	4.2	NA
Docetaxel/trastuzumab (82)	Phase II	57	SDC	HER2	70	8.9	39.7
Docetaxel/trastuzumab (83)	Phase II	16	SDC	HER2	60	8.5	NR
Trastuzumab/pertuzumab (84)	Phase IIa	15	Any	HER2	60	8.6	20.4
Trastuzumab emtansine (86)	Phase II	10	SDC/ANOS*	HER2	90	NR	NR
Trastuzumab deruxtecan (86)	Phase I (pool)	17	SDC*	HER2	47	14.1	NA
Entrectinib (90)	Phase I/II	7	SC*	NTRK	86	NA	NA
Larotectinib (91)	Phase I/II	12	SC*	NTRK	90	NA	NA

*Subgroup analysis

ANOS, adenocarcinoma, not otherwise specified; AR, androgen receptor; LHRHa, leuteinizing hormone-releasing hormone agonist; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; NR, not reached; ORR, objective response rate; SC, secretory carcinoma; SDC, salivary duct carcinoma

Table 8. Clinical studies of immune checkpoint inhibitors for recurrent/metastatic salivary gland malignancies

Treatment	Study design	N	Histology (%)	PD-L1, N (%)	ORR (%)	mPFS (M)	mOS (M)
Nivolumab (95)	Retrospective	22	NA	NA	14	2.1	NR (10.3+)
Nivolumab (96)	Retrospective	24	SDC (83)	11 (46)	4	1.6	10.7
Nivolumab (97)	Phase II	45	AdCC	NA	9	4.9	18.1
Nivolumab (97)	Phase II	50	Non-AdCC	NA	4	1.8	9.5
Pembrolizumab (98)	Phase Ib	26	Non-AdCC (92)	26 (100)	12	4	13
Pembrolizumab ± RT (90)	Randomized phase II	20	AdCC	11/16 (69)	0	6.6*	27.2*
Nivolumab/ipilimumab (100)	Phase II	32	AdCC	6	6	4.4	NA
Nivolumab/ipilimumab (101)	Phase II	32	Non-AdCC	NA	16	2.3	NA
Pembrolizumab/vorinostat (102)	Phase I/II	25	12 AdCC (48)	4/21(19)	16	4.5	12.6

*Pembrolizumab-alone

AdCC, adenoid cystic carcinoma; AR, androgen receptor; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; NR, not reached; ORR, objective response rate; RT, radiotherapy; SDC, salivary duct carcinoma

Table 9. Featured ongoing clinical trials for recurrent/metastatic salivary gland malignancies

Treatment	Trial number	Trial design	N	Histology	Target
AL101	NCT03691207	Phase II	87	AdCC	NOTCH
Surufatinib	NCT05013515	Phase II	27	ANOS	VEGFR/FGFR/CSF-1R
Lutetium-177-PMSA	NCT04291300	Phase II	10	Cohort1: AdCC Cohort2: SDC	Prostate specific membrane antigen
Bicalutamide/triptorelin (vs cisplatin/docetaxel or carboplatin/paclitaxel)	NCT01969578	Randomized phase II	76	SDC/ANOS	Androgen receptor
Apalutamide/goserelin	JapicCTI-205249	Phase II	24	SDC/ANOS	Androgen receptor
Darolutamide	jRCT2031190241	Phase II	24	SDC/ANOS	Androgen receptor
Nivolumab	UMIN000029636	Phase II	24*	Any	-
Nivolumab/ipilimumab+SABR	NCT03749460	Phase II	20	Any	-
Docetaxel/pembrolizumab	NCT03360890	Phase II	46**	Any	-
Pemetrexed/pembrolizumab	NCT04895735	Phase II	45	Any	-
Goserelin/pembrolizumab	NCT03942653	Phase II	20	Any	Androgen receptor
Lenvatinib/pembrolizumab	NCT04209660	Phase II	64	Any	-

* Participants include all non-squamous-cell head and neck cancer.

** Participants include both salivary gland malignancies and thyroid cancer.

AdCC, adenoid cystic carcinoma; ANOS, adenocarcinoma, not otherwise specified; SABR, stereotactic ablative body radiotherapy; SDC, salivary duct carcinoma