# 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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## References


1. Guzzo M, Locati LD, Prott FJ et al. Major and minor salivary gland tumors. Crit Rev Oncol Hematol 2010; 74 (2): 134-148.
2. Skalova A, Stenman G, Simpson RH, Hellquist H, Slouka D, Svoboda T, et al. The Role of Molecular Testing in the Differential Diagnosis of Salivary Gland Carcinomas. Am J Surg Pathol 2018; 42 (2): e11-e27.
3. El-Naggar AK, Chan JKC, et al. Tumours of salivary glands, in WHO Classification of Head and Neck Tumours (ed 4). Lyon, France, IARC Press, 2017, p 159.
4. Geiger JL, Ismaila N, Beadle B et al. Management of Salivary Gland Malignancy: ASCO Guideline. J Clin Oncol 2021; 39 (17): 1909-1941.
5. Son E, Panwar A, Mosher CH, et al. Cancers of the Major Salivary Gland. J Oncol Pract 2018; 14(2): 99-108.
6. Lin HH, Limesand KH, and Ann DK. Current State of Knowledge on Salivary Gland Cancers. Crit Rev Oncog 2018; 23 (3-4): 139-151.
7. Skalova A, Michal M, and Simpson RH. Newly described salivary gland tumors. Mod Pathol 2017; 30 (s1): S27-S43.
8. Mahmood U, Koshy M, Goloubeva O et al. Adjuvant radiation therapy for high-grade and/or locally advanced major salivary gland tumors. Arch Otolaryngol Head Neck Surg 2011; 137 (10):

1025-1030.

9. Safdieh J, Givi B, Osborn V et al. Impact of Adjuvant Radiotherapy for Malignant Salivary Gland Tumors. Otolaryngol Head Neck Surg 2017; 157 (6): 988-994.

10. Cheraghlou S, Kuo P, Mehra S et al. Adjuvant therapy in major salivary gland cancers: Analysis of 8580 patients in the National Cancer Database. Head Neck 2018; 40 (7): 1343-1355.

11. Cheraghlou S, Schettino A, Zogg CK et al. Adjuvant Chemotherapy Is Associated With Improved Survival for Late-Stage Salivary Squamous Cell Carcinoma. Laryngoscope 2019; 129 (4): 883-889.

12. Hsieh CE, Lin CY, Lee LY et al. Adding concurrent chemotherapy to postoperative radiotherapy improves locoregional control but Not overall survival in patients with salivary gland adenoid cystic carcinoma-a propensity score matched study. Radiat Oncol 2016; 11: 47.

13. Mifsud MJ, Tanvetyanon T, McCaffrey JC et al. Adjuvant radiotherapy versus concurrent chemoradiotherapy for the management of high-risk salivary gland carcinomas. Head Neck 2016; 38 (11): 1628-1633.

14. Amini A, Waxweiler TV, Brower JV et al. Association of Adjuvant Chemoradiotherapy vs Radiotherapy Alone With Survival in Patients With Resected Major Salivary Gland Carcinoma: Data From the National Cancer Data Base. JAMA Otolaryngol Head Neck Surg 2016; 142 (11): 1100-1110.

306 15. Osborn V, Givi B, Lee A et al. Characterization, treatment and outcomes of salivary ductal
307 carcinoma using the National Cancer Database. Oral Oncol 2017; 71: 41-46.
308 16. Gebhardt BJ, Ohr JP, Ferris RL et al. Concurrent Chemoradiotherapy in the Adjuvant Treatment
309 of High-risk Primary Salivary Gland Malignancies. Am J Clin Oncol 2018; 41 (9): 888-893.
310 17. Tanvetyanon T, Fisher K, Caudell J et al. Adjuvant chemoradiotherapy versus with radiotherapy
311 alone for locally advanced salivary gland carcinoma among older patients. Head Neck 2016; 38
312 (6): 863-870.
313 18. Bernier J, Cooper JS, Pajak TF et al. Defining risk levels in locally advanced head and neck
314 cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of
315 the EORTC (#22931) and RTOG (# 9501). Head Neck 2005; 27 (10): 843-850.
316 19. van Boxtel W, Locati LD, van Engen-van Grunsven ACH et al. Adjuvant androgen deprivation
317 therapy for poor-risk, androgen receptor-positive salivary duct carcinoma. Eur J Cancer 2019;
318 110: 62-70.
319 20. Limaye SA, Posner MR, Krane JF et al. Trastuzumab for the treatment of salivary duct carcinoma.
320 Oncologist 2013; 18 (3): 294-300.
321 21. Hanna GJ, Bae JE, Lorch JH et al. The Benefits of Adjuvant Trastuzumab for HER-2-Positive
322 Salivary Gland Cancers. Oncologist 2020; 25 (7): 598-608.
323 22. Rosenberg L, Weissler M, Hayes DN et al. Concurrent chemoradiotherapy for locoregionally

advanced salivary gland malignancies. Head Neck 2012; 34 (6): 872-876.

23. Katori H, Tsukuda M. Concurrent chemoradiotherapy with cyclophosphamide, pirarubicin, and cisplatin for patients with locally advanced salivary gland carcinoma. Acta Otolaryngol 2006; 126 (12): 1309-1314.

24. Bhattasali O, Holliday E, Kies MS et al. Definitive proton radiation therapy and concurrent cisplatin for unresectable head and neck adenoid cystic carcinoma: A series of 9 cases and a critical review of the literature. Head Neck 2016; 38 Suppl 1: E1472-1480.

25. Haddad RI, Posner MR, Busse PM, et al. Chemoradiotherapy for adenoid cystic carcinoma: preliminary results of an organ sparing approach Am J Clin Oncol 2006; 29 (2): 153-157.

26. Samant S, van den Brekel MW, Kies MS et al. Concurrent chemoradiation for adenoid cystic carcinoma of the head and neck. Head Neck 2012; 34 (9): 1263-1268.

27. Lievens Y, Guckenberger M, Gomez D et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiother Oncol 2020; 148: 157-166.

28. Girelli L, Locati L, Galeone C et al. Lung metastasectomy in adenoid cystic cancer: Is it worth it? Oral Oncol 2017; 65: 114-118.

29. Locati LD, Guzzo M, Bossi P et al. Lung metastasectomy in adenoid cystic carcinoma (ACC) of salivary gland. Oral Oncol 2005; 41 (9): 890-894.

342 30. Bobbio A, Copelli C, Ampollini L et al. Lung metastasis resection of adenoid cystic carcinoma of
343 salivary glands. Eur J Cardiothorac Surg 2008; 33 (5): 790-793.
344 31. Licitra L, Marchini S, Spinazze S et al. Cisplatin in advanced salivary gland carcinoma. A phase
345 II study of 25 patients. Cancer 1991; 68 (9): 1874-1877.
346 32. Vermorken JB, Verweij J, de Mulder PH et al. Epirubicin in patients with advanced or recurrent
347 adenoid cystic carcinoma of the head and neck: a phase II study of the EORTC Head and Neck
348 Cancer Cooperative Group. Ann Oncol 1993; 4 (9): 785-788.
349 33. Mattox DE, Von Hoff DD, Balcerzak SP. Southwest Oncology Group study of mitoxantrone for
350 treatment of patients with advanced adenoid cystic carcinoma of the head and neck. Invest New
351 Drugs 1990; 8 (1): 105-107.
352 34. Gilbert J, Li Y, Pinto HA et al. Phase II trial of taxol in salivary gland malignancies (E1394): a
353 trial of the Eastern Cooperative Oncology Group. Head Neck 2006; 28 (3): 197-204.
354 35. Van Herpen CM, Locati LD, Buter J, et al. Phase II study on gemcitabine in recurrent and/or
355 metastatic adenoid cystic carcinoma of the head and neck (EORTC 24982). Eur J Cancer 2008;
356 44 (17): 2542–2545.
357 36. Airoldi M, Pedani F, Succo G et al. Phase II randomized trial comparing vinorelbine versus
358 vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies. Cancer 2001; 91
359 (3): 541-547.

360 37. Airoldi M, Garzaro M, Pedani F et al. Cisplatin+Vinorelbine Treatment of Recurrent or Metastatic
361 Salivary Gland Malignancies (RMSGM): A Final Report on 60 Cases. Am J Clin Oncol 2017; 40
362 (1): 86-90.
363 38. Hong MH, Kim CG, Koh YW et al. Efficacy and safety of vinorelbine plus cisplatin chemotherapy
364 for patients with recurrent and/or metastatic salivary gland cancer of the head and neck. Head
365 Neck 2018; 40 (1): 55-62.
366 39. Licitra L, Cavina R, Grandi C et al. Cisplatin, doxorubicin and cyclophosphamide in advanced
367 salivary gland carcinoma. A phase II trial of 22 patients. Ann Oncol 1996; 7 (6): 640-642.
368 40. Alberts DS, Manning MR, Coulthard SW et al. Adriamycin/cis-platinum/cyclophosphamide
369 combination chemotherapy for advanced carcinoma of the parotid gland. Cancer 1981; 47 (4):
370 645-648.
371 41. Kaplan MJ, Johns ME, Cantrell RW. Chemotherapy for salivary gland cancer. Otolaryngol Head
372 Neck Surg 1986; 95 (2): 165-170.
373 42. Belani CP, Eisenberger MA, Gray WC. Preliminary experience with chemotherapy in advanced
374 salivary gland neoplasms. Med Pediatr Oncol 1988; 16 (3): 197-202.
375 43. Dreyfuss AI, Clark JR, Fallon BG et al. Cyclophosphamide, doxorubicin, and cisplatin
376 combination chemotherapy for advanced carcinomas of salivary gland origin. Cancer 1987; 60
377 (12): 2869-2872.

44. Creagan ET, Woods JE, Rubin J et al. Cisplatin-based chemotherapy for neoplasms arising from salivary glands and contiguous structures in the head and neck. Cancer 1988; 62 (11): 2313-2319.

45. Airoldi M, Fornari G, Pedani F, et al. Paclitaxel and carboplatin for recurrent salivary gland malignancies. Anticancer Res 2000; 20 (5C): 3781-3783.

46. Imamura Y, Kiyota N, Tanaka K, et al. A phase II trial of docetaxel plus cisplatin in recurrent and/or metastatic non-squamous cell carcinoma of head and neck. Medical Oncol 2021; 38: 128.

47. Okada T, Saotome T, Nagao T, et al. Carboplatin and Docetaxel in Patients With Salivary Gland Carcinoma: A Retrospective Study. In Vivo 2019; 33 (3): 843-853.

48. Nakano K, Sato Y, Sasaki T et al. Combination chemotherapy of carboplatin and paclitaxel for advanced/metastatic salivary gland carcinoma patients: differences in responses by different pathological diagnoses. Acta Otolaryngol 2016; 136 (9): 948-951.

49. Alfieri S, Granata R, Bergamini C, et al. Systemic therapy in metastatic salivary gland carcinomas: A pathology-driven paradigm? Oral Oncol 2017; 66: 58-63.

50. Locati LD, Perrone F, Losa M et al. Treatment relevant target immunophenotyping of 139 salivary gland carcinomas (SGCs). Oral Oncol 2009; 45 (11): 986-990.

51. Skalova A, Vanecek T, Sima R et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. Am J Surg Pathol 2010; 34 (5): 599-608.

396 52. Pfeffer MR, Talmi Y, Catane R et al. A phase II study of Imatinib for advanced adenoid cystic
397 carcinoma of head and neck salivary glands. Oral Oncol 2007; 43 (1): 33-36.
398 53. Hotte SJ, Winquist EW, Lamont E et al. Imatinib mesylate in patients with adenoid cystic cancers
399 of the salivary glands expressing c-kit: a Princess Margaret Hospital phase II consortium study. J
400 Clin Oncol 2005; 23 (3): 585-590.
401 54. Guigay JM, Bidault F, Temam S, et al. Antitumor activity of imatinib in progressive, highly
402 expressing KIT adenoid cystic carcinoma of the salivary glands: A phase II study. J Clin Oncol
403 2007; 25 [suppl abstr 6086].
404 55. Wong SJ, Karrison T, Hayes DN et al. Phase II trial of dasatinib for recurrent or metastatic c-KIT
405 expressing adenoid cystic carcinoma and for nonadenoid cystic malignant salivary tumors. Ann
406 Oncol 2016; 27 (2): 318-323.
407 56. Agulnik M, Cohen EW, Cohen RB, et al. Phase II study of lapatinib in recurrent or metastatic
408 epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non
409 adenoid cystic carcinoma malignant tumors of the salivary glands. J Clin Oncol 2007; 25 (25):
410 3978-3984.
411 57. Jakob JA, Kies MS, Glisson BS et al. Phase II study of gefitinib in patients with advanced salivary
412 gland cancers. Head Neck 2015; 37 (5): 644-649.
413 58. Locati LD, Bossi P, Perrone F et al. Cetuximab in recurrent and/or metastatic salivary gland

carcinomas: A phase II study. Oral Oncol 2009; 45 (7): 574-578.

59. Kim DW, Oh DY, Shin SH et al. A multicenter phase II study of everolimus in patients with progressive unresectable adenoid cystic carcinoma. BMC Cancer 2014; 14: 795.

60. Hoover AC, Milhem MM, Anderson CM et al. Efficacy of nelfinavir as monotherapy in refractory adenoid cystic carcinoma: Results of a phase II clinical trial. Head Neck 2015; 37 (5): 722-726.

61. Ho AL, Foster NR, Meyers JP, et al. Alliance A091104: A phase II trial of MK-2206 in patients (pts) with progressive, recurrent/metastatic adenoid cystic carcinoma. J Clin Oncol 2015; 33 [suppl abstr 6039].

62. van Boxtel W, Uijen MJM, Krens S, et al. Excessive toxicity of cabozantinib in a phase II study in patients with recurrent and/or metastatic salivary gland cancer. Eur J Cancer. 2021; S0959-8049(21)01191-6.

63. Tchekmedyian V, Sherman EJ, Dunn L et al. Phase II Study of Lenvatinib in Patients With Progressive, Recurrent or Metastatic Adenoid Cystic Carcinoma. J Clin Oncol 2019; 37 (18): 1529-1537.

64. Locati LD, Galbiati D, Calareso G et al. Patients with adenoid cystic carcinomas of the salivary glands treated with lenvatinib: Activity and quality of life. Cancer 2020; 126 (9): 1888-1894.

65. Thomson DJ, Silva P, Denton K et al. Phase II trial of sorafenib in advanced salivary adenoid cystic carcinoma of the head and neck. Head Neck 2015; 37 (2): 182-187.

66. Locati LD, Perrone F, Cortelazzi B et al. A phase II study of sorafenib in recurrent and/or metastatic salivary gland carcinomas: Translational analyses and clinical impact. Eur J Cancer 2016; 69: 158-165.

67. Ho AL, Dunn L, Sherman EJ et al. A phase II study of axitinib (AG-013736) in patients with incurable adenoid cystic carcinoma. Ann Oncol 2016; 27 (10): 1902-1908.

68. Locati LD, Cavalieri S, Bergamini C et al. Phase II trial with axitinib in recurrent and/or metastatic salivary gland cancers of the upper aerodigestive tract. Head Neck 2019; 41 (10): 3670-3676.

69. Keam B, Kang EJ, Ahn MJ, et al. Randomized phase II study of axitinib versus observation in patients with recurred or metastatic adenoid cystic carcinoma. J Clin Oncol 2020; 38 [suppl abstr 6503].

70. Chau NG, Hotte SJ, Chen EX et al. A phase II study of sunitinib in recurrent and/or metastatic adenoid cystic carcinoma (ACC) of the salivary glands: current progress and challenges in evaluating molecularly targeted agents in ACC. Ann Oncol 2012; 23 (6): 1562-1570.

71. Kim Y, Lee SJ, Lee JY et al. Clinical trial of nintedanib in patients with recurrent or metastatic salivary gland cancer of the head and neck: A multicenter phase 2 study (Korean Cancer Study Group HN14-01). Cancer 2017; 123 (11): 1958-1964.

72. Guigay J, Fayette J, Even C, et al. PACSA: Phase II study of pazopanib in patients with progressive recurrent or metastatic (R/M) salivary gland carcinoma (SGC). J Clin Oncol 2016; 34

[suppl abstr 6086].

73. Ho AL, Sherman EJ, Baxi SS, et al. Phase II study of regorafenib in progressive, recurrent/metastatic adenoid cystic carcinoma. J Clin Oncol 2016; 34 [suppl; abstr 6096].

74. Boon E, van Boxtel W, Buter J et al. Androgen deprivation therapy for androgen receptor-positive advanced salivary duct carcinoma: A nationwide case series of 35 patients in The Netherlands. Head Neck 2018; 40 (3): 605-613.

75. Fushimi C, Tada Y, Takahashi H et al. A prospective phase II study of combined androgen blockade in patients with androgen receptor-positive metastatic or locally advanced unresectable salivary gland carcinoma. Ann Oncol 2018; 29 (4): 979-984.

76. Viscuse PV, Price KA, Garcia JJ et al. First Line Androgen Deprivation Therapy vs. Chemotherapy for Patients With Androgen Receptor Positive Recurrent or Metastatic Salivary Gland Carcinoma-A Retrospective Study. Front Oncol 2019; 9: 701.

77. Locati LD, Perrone F, Cortelazzi B et al. Clinical activity of androgen deprivation therapy in patients with metastatic/relapsed androgen receptor-positive salivary gland cancers. Head Neck 2016; 38 (5): 724-731.

78. Jaspers HC, Verbist BM, Schoffelen R et al. Androgen receptor-positive salivary duct carcinoma: a disease entity with promising new treatment options. J Clin Oncol 2011; 29 (16): e473-476.

79. Yajima Y, Fujii S, Kobayashi T, et al. Anti-androgen therapy for patients with recurrent and/or

metastatic salivary duct carcinoma expressing androgen receptors: a retrospective study. Ann Oncol 2012; 23 [suppl 9 (abstract 1706P)].

80. Ho AL, Foster NR, Zoroufy AJ, et al. Alliance A091404: A phase II study of enzalutamide (NSC# 766085) for patients with androgen receptor-positive salivary cancers. J Clin Oncol 2019; 37 [suppl abstr 6020].

81. Locati LD, Cavalieri S, Bergamini C, et al. Abiraterone Acetate in Patients With Castration-Resistant, Androgen Receptor-Expressing Salivary Gland Cancer: A Phase II Trial. J Clin Oncol 2021; 39 (36): 4061-4068.

82. Takahashi H, Tada Y, Saotome T et al. Phase II Trial of Trastuzumab and Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2-Positive Salivary Duct Carcinoma. J Clin Oncol 2019; 37 (2): 125-134.

83. Ichiro Kinoshita I. Kano S, Satoshi Shimizu Y, et al. Phase II study of trastuzumab and docetaxel therapy in patients with HER2-positive recurrent and/or metastatic salivary gland carcinoma. Cancer Res 2019; 79 (13 Suppl): Abstract nr CT137.

84. Kurzrock R, Bowles DW, Kang H et al. Targeted therapy for advanced salivary gland carcinoma based on molecular profiling: results from MyPathway, a phase IIa multiple basket study. Ann Oncol 2020; 31 (3): 412-421.

85. Haddad R, Colevas AD, Krane JF, Cooper D, Glisson B, Amrein PC, et al. Herceptin in patients

with advanced or metastatic salivary gland carcinomas. A phase II study. Oral Oncol 2003; 39 (7): 724-727.

86. Li BT, Shen R, Offin M, et al. Ado-trastuzumab emtansine in patients with HER2 amplified salivary gland cancers (SGCs): Results from a phase II basket trial. J Clin Oncol 2019; 37 [suppl abstr 6001].

87. Bando H, Kinoshita I, Modi S, et al. Trastuzumab deruxtecan (T-DXd) in patients with human epidermal growth factor receptor 2 (HER2)-expressing salivary duct carcinoma: Subgroup analysis of two phase 1 studies. J Clin Oncol 2021; 39 [suppl abstr 6079].

88. Luk PP, Selinger CI, Eviston TJ, Lum T, Yu B, O'Toole SA, et al. Mammary analogue secretory carcinoma: an evaluation of its clinicopathological and genetic characteristics. Pathology 2015; 47 (7): 659-666.

89. Inaki R, Abe M, Zong L, Abe T, Shinozaki-Ushiku A, Ushiku T, et al. Secretory carcinoma - impact of translocation and gene fusions on salivary gland tumor. Chin J Cancer Res 2017; 29(5): 379-384.

90. Doebele RC, Drilon A, Paz-Ares L et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020; 21 (2): 271-282.

91. Hong DS, DuBois SG, Kummar S et al. Larotrectinib in patients with TRK fusion-positive solid

504 tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020; 21 (4): 531-540.

505 92. Majewska H, Gorczynski A, Czapiewski P et al. ALK alterations in salivary gland carcinomas.

506 Virchows Arch 2021; 478 (5): 933-941.

507 93. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With

508 Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From

509 the Phase II KEYNOTE-158 Study. J Clin Oncol 2020; 38 (1): 1-10.

510 94. Le DT, Durham JN , Smith KN, et al. Mismatch repair deficiency predicts response of solid

511 tumors to PD-1 blockade. Science 2017; 357 (6349); 409-413.

512 95. Hanai N, Shimizu Y, Kariya S et al. Effectiveness and safety of nivolumab in patients with head

513 and neck cancer in Japanese real-world clinical practice: a multicenter retrospective clinical study.

514 Int J Clin Oncol 2021; 26 (3): 494-506.

515 96. Niwa K, Kawakita D, Nagao T et al. Multicentre, retrospective study of the efficacy and safety of

516 nivolumab for recurrent and metastatic salivary gland carcinoma. Sci Rep 2020; 10 (1): 16988.

517 97. Fayette J, Even C, Digue L, et al. NISCAHN: Phase II Study of Nivolumab in Patients With

518 Progressive Recurrent or Metastatic Salivary Glands Carcinoma. J Clin Oncol 2019; 37 [suppl

519 abstr 6083].

520 98. Cohen RB, Delord JP, Doi T et al. Pembrolizumab for the Treatment of Advanced Salivary Gland

521 Carcinoma: Findings of the Phase 1b KEYNOTE-028 Study. Am J Clin Oncol 2018; 41 (11):

1083-1088.

99. Mahmood U, Bang A, Chen YH et al. A Randomized Phase 2 Study of Pembrolizumab With or Without Radiation in Patients With Recurrent or Metastatic Adenoid Cystic Carcinoma. Int J Radiat Oncol Biol Phys 2021; 109 (1): 134-144.

100. Tchekmedyian V, Sherman EJ, Dunn L, et al. A phase II trial cohort of nivolumab plus ipilimumab in patients (Pts) with recurrent/metastatic adenoid cystic carcinoma (R/M ACC). J Clin Oncol 2019; 37 [suppl abstr 6084].

101. Burman B, Sherman EJ, Dunn L, et al. A phase II trial cohort of nivolumab plus ipilimumab in patients (Pts) with recurrent/metastatic salivary gland cancers (R/M SGCs). J Clin Oncol 2021; 39 [suppl abstr 6002].

102. Rodriguez CP, Wu QV, Voutsinas J et al. A Phase II Trial of Pembrolizumab and Vorinostat in Recurrent Metastatic Head and Neck Squamous Cell Carcinomas and Salivary Gland Cancer. Clin Cancer Res 2020; 26 (4): 837-845.

103. Ott PA, Hodi FS, Kaufman HL et al. Combination immunotherapy: a road map. J Immunother Cancer 2017; 5: 16.

104. Hill ME, Constenla DO, A'Hern RP et al. Cisplatin and 5-fluorouracil for symptom control in advanced salivary adenoid cystic carcinoma. Oral Oncol 1997; 33 (4): 275-278.

105. Dimery IW, Legha SS, Shirinian M et al. Fluorouracil, doxorubicin, cyclophosphamide, and

cisplatin combination chemotherapy in advanced or recurrent salivary gland carcinoma. J Clin Oncol 1990; 8 (6): 1056-1062.

106. Laurie SA, Siu LL, Winquist E, et al. A phase 2 study of platinum and gemcitabine in patients with advanced salivary gland cancer: a trial of the NCIC Clinical Trials Group. Cancer 2010; 116 (2): 362-368.

107. Argiris A, Ghebremichael M, Burtness B et al. A phase 2 trial of bortezomib followed by the addition of doxorubicin at progression in patients with recurrent or metastatic adenoid cystic carcinoma of the head and neck: a trial of the Eastern Cooperative Oncology Group (E1303). Cancer 2011; 117 (15): 3374-3382.

108. Keam B, Kim SB, Shin SH et al. Phase 2 study of dovitinib in patients with metastatic or unresectable adenoid cystic carcinoma. Cancer 2015; 121 (15): 2612-2617.

109. Dillon PM, Petroni GR, Horton BJ et al. A Phase II Study of Dovitinib in Patients with Recurrent or Metastatic Adenoid Cystic Carcinoma. Clin Cancer Res 2017; 23 (15): 4138-4145.

110. Goncalves PH, Heilbrun LK, Barrett MT et al. A phase 2 study of vorinostat in locally advanced, recurrent, or metastatic adenoid cystic carcinoma. Oncotarget 2017; 8 (20): 32918-32929.

111. Hanna GJ, Guenette JP, Chau NG, et al. Tipifarnib in recurrent, metastatic HRAS-mutant salivary gland cancer. Cancer 2020; 126 (17): 3972-3981.

558 112. Hanna GJ, A ON, Cutler JM et al. A phase II trial of all-trans retinoic acid (ATRA) in
559 advanced adenoid cystic carcinoma. Oral Oncol 2021; 119: 105366.

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)<br>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)<br>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)<br>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<br>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)<br>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)<br>HR 0.14 (0.03-0.75) | -<br>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<br>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