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ORIGINAL RESEARCH

Systemic treatments in recurrent or metastatic salivary gland cancer: a systematic review

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Available online xxx

Background: Salivary gland cancers are infrequent and pose a challenge owing to their histological diversity and varied clinical behavior, making the selection of optimal systemic treatments for advanced or recurrent stages difficult. This systematic review aims to assess overall survival outcomes and systemic treatment responses across four types of salivary cancers.

Methods: A PubMed and Google Scholar search identified studies involving initially advanced or relapsed cases undergoing systemic treatment. Studies with clear, individualized data on treatment responses and outcomes were selected based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Of the 723 studies screened, 44 met our inclusion criteria.

Results: A total of 426 cases of recurrent/metastatic salivary gland cancer, mostly salivary duct carcinoma (SDC; $n = 219$) and adenoid cyst carcinoma (ACC; $n = 167$), were included. Histomolecular markers were heavily associated with histology, with *HER2* overexpression and androgen receptor nuclear expression typically found in SDC and adenocarcinoma not otherwise specified cases and KIT overexpression only in ACC. The response rates were associated with specific receptor blockage, with trastuzumab plus chemotherapy, and bicalutamide being the most effective (overall response rate 80% and 42.8%, respectively). Moreover, the response to treatment positively influenced overall survival (responders 38 versus non-responders 18.7 median months; $P < 0.001$). In this retrospective analysis of a particular cohort, survival outcomes per histology types showed that anti-human epidermal growth factor receptor 2 therapy was more effective for SDC, while chemotherapy was more effective for ACC.

Conclusion: Systemic treatments contribute to the survival of patients with salivary gland cancer at relapsed or newly advanced stages. The response to treatment is heavily influenced by histological subtype and treatment specificity.

Key words: salivary gland cancer, systematic review, anti-HER2, androgen deprivation therapy

INTRODUCTION

Salivary gland carcinomas represent ∼20% of all salivary gland tumors and are characterized by substantial clinical, histological, and molecular heterogeneity.[1,2] These malignancies can arise from any major or minor salivary glands and predominantly affect middle-aged men, exhibiting diverse histological subtypes and histotype-specific molecular markers, including androgen receptor (AR), *HER2*, *PI3KCA*.[3-11]

The clinical presentation of salivary gland carcinomas poses a challenge, with some tumors demonstrating rapid progression through multiple lines of treatment, whereas others remain stable despite the presence of metastatic disease.[12-15] While local initially or recurrent disease is usually managed through tumor resection followed by adjuvant radiotherapy, the optimal systemic treatment modalities for recurrent or metastatic salivary gland carcinomas remain uncertain.[16,17] Frequently, chemotherapy combinations,[18-21] *HER2* inhibitors or androgen deprivation therapy (ADT)[22-30] are indicated with different outcomes, although the lack of advanced trials comparing strategies is notable.

Despite the abundance of clinical data, there exists a gap in knowledge regarding optimal systemic treatment options, especially for salivary gland carcinomas with different

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histology and molecular drivers.[20,22-29] It remains unclear if treatment has a significant impact on the survival outcomes, and a systematic comparison between these subtypes has yet to be conducted.

In this systematic review, we have gathered information from 44 studies[18,23-26,30-68] (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103722) and individualized data from 426 cases of recurrent or metastatic salivary gland carcinomas treated with systemic therapy. We have included publications that provide data on treatment response and outcomes in adenoid cyst carcinoma (ACC), salivary duct carcinoma (SDC), mucoepidermoid carcinoma, and adenocarcinoma not otherwise specified (NOS) histology. The treatments analyzed encompass ADT, anti-human epidermal growth factor receptor 2 (anti-HER2) therapy, chemotherapy, tyrosine kinase inhibitors (TKIs), and immunotherapy. Our primary objectives were to analyze treatment response and outcomes for comparable cases receiving specific and nonspecific targeted treatments.

METHODS

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[68,69] and the reporting recommendations for tumor marker prognostic studies (REMARK) were followed.[70] The primary endpoints for this review were (i) response to different types of treatment modalities and (ii) the overall survival for a subset of cases without previous systemic treatment.

Search strategies and data extraction

We conducted a bibliographical search using PubMed and Google Scholar with the following codes: 'salivary gland cancer treatment', 'salivary gland chemotherapy', 'salivary gland androgen', 'salivary gland *HER2*', 'salivary gland TKI', 'salivary gland immunotherapy'. We also allowed articles by manual search. Articles published from 1 January 1990, to 1 October 2023, only in English language were considered. The proposal was registered *a priori* at the National Institute for Health Research, (PROSPERO; under the registration number: CRD42023391655).

Study selection criteria were adjusted to reduce the risk of bias: (i) papers which included ACC, ductal, mucoepidermoid or adenocarcinoma NOS salivary gland cancer patients for a systemic treatment (e.g. paclitaxel, sorafenib, pembrolizumab); (ii) available information for overall survival and best radiological response; (iii) and individualized data (Figure 1). Papers lacking suitable data underwent a separation process for subsequent contact with the authors. Additionally, data extraction from published graphics was permitted during this phase. Studies reported in conference abstracts, medical meetings, studies including radiotherapy as intervention or studies with insufficient data were excluded.

Data was extracted by the two reviewers (DP and ER) and registered in a Microsoft Excel file. Information collected included: demographics and molecular features, surgical treatment, previous systemic treatment, treatment, best radiological response, and overall survival. All data extracted were quality checked and reviewed once the data extraction was completed by the same two reviewers (DP and ER). Cases reported with molecular features (e.g. *HER2*, AR) rarely associated with ACC or mucoepidermoid[10] histology were excluded to avoid overrepresentation of extremely infrequent presentations.

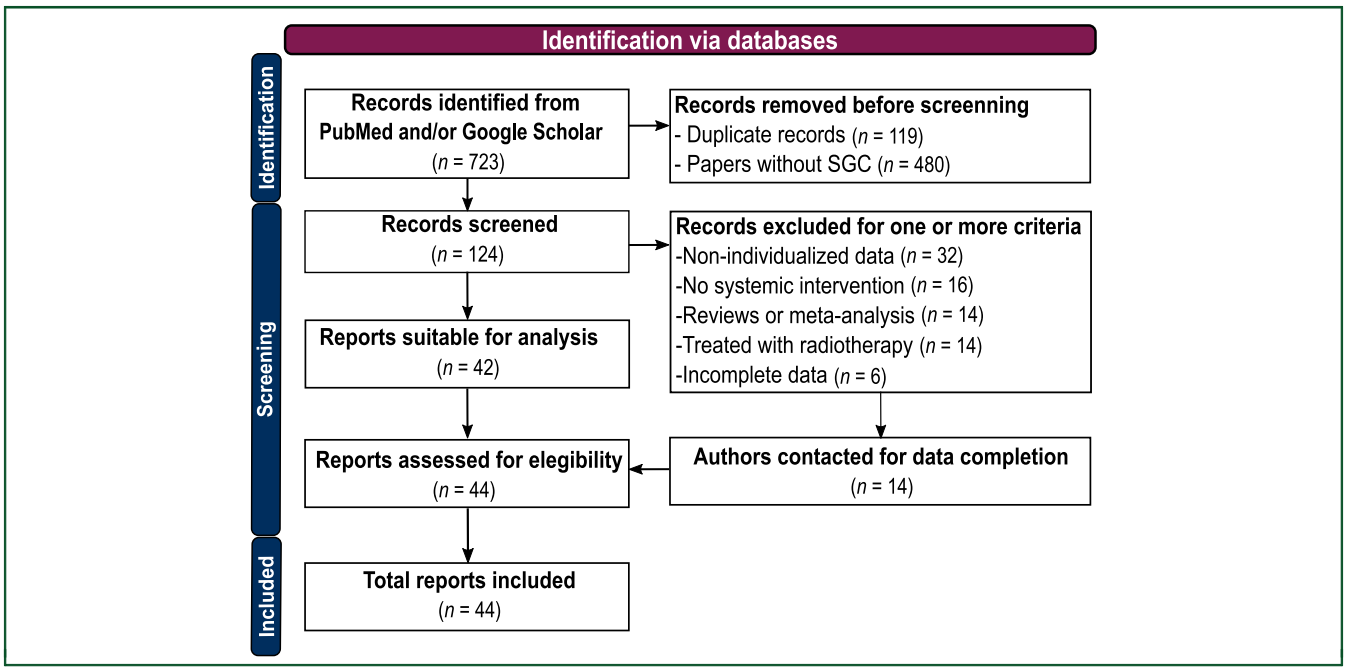

Figure 1. CONSORT diagram illustrating the selection process of reports identified for the systematic review. The most frequent absence of data in identified records was related to response or survival after treatment, as well individualized data for case series or early-phase trials. Fourteen authors were consulted to complete missing data, resulting in the inclusion of two additional trials after consultation.
SGC, salivary gland cancer.

Summary measures, synthesis, and statistical analysis

We produced a review, reporting molecular and clinical characteristics as well as best radiological response and outcome, defining overall survival from the moment of treatment to death by any cause in all the studies. The results were described by cancer type and treatment received. Associations between categorical variables were tested with the Fisher's exact test. Using Kaplan−Meier estimates, the median overall survival with 95% confidence intervals (CIs) was determined. A log-rank test and Cox's regression model were carried out to compare differences in survival. Analyses and graphical work were created using packages (e.g. ggplot2[71]; juicr[72]) and R version 4.1.2 (2022-07-01, Boston, MA).

RESULTS

In our final analysis, we included a cohort of 426 salivary gland cases with a median age of 56 years, predominantly men with distant metastasis (Table 1). The prevailing cancers type were SDC ($n = 219$), followed by ACC ($n = 167$), adenocarcinoma NOS ($n = 23$), and mucoepidermoid ($n = 17$). A considerable proportion of cases (55%) exhibited some molecular features, with distribution clearly influenced by histology. Specifically, SDC and adenocarcinoma NOS demonstrated *HER2* overexpression and/or amplification (53.8% and 47.8%, respectively), and AR nuclear expression (48.7% and 30.4%, respectively). Other less frequent mutations (<5%) such as *PI3KCA*, *BRAF*, and *PTCH-1* were also predominant in SDC and adenocarcinoma NOS, while *RAS*, as expected, was also high in mucoepidermoid carcinomas ($n = 5/17$). In contrast, ACC was characterized by the near absence of markers except for *KIT* overexpression (16%). The response to any type of treatment was also highly determined by histology being <10% of all ACC cases versus 30%-40% for the rest (Figure 2).

The analysis of various treatments across histological subtypes revealed no definitive advantage for any single modality, although several notable patterns emerged. Here, we describe the responses obtained for the four types of cancer included (see Figure 3A and Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103722).

SDC, being the most prevalent histology among the included types, experienced anti-HER2 therapy as the most frequently employed treatment ($n = 96$). Trastuzumab, often combined with chemotherapy, primarily taxanes, demonstrated the most extensive administrated and yielded a robust response in SDC cases [$n = 73$, overall response rate (ORR) 79%]. Other combinations such as trastuzumab plus pertuzumab ($n = 10/14$) or trastuzumab emtansine ($n = 4/7$) showed responses in both first-line and subsequent treatments, albeit in a smaller number of SDC cases.

Additionally, 74 SDC cases underwent ADT. Enzalutamide ($n = 41$), abiraterone ($n = 19$), and bicalutamide ($n = 14$) were among the agents utilized. Notably, despite previous ADT exposure in some cases, seven patients showed a response to enzalutamide (ORR 17%). Combinations such as abiraterone plus leuprolide ($n = 19$) and bicalutamide ± leuprolide ($n = 14$) also elicited responses in a subset of patients, some of whom were treated after initial progression.

A particularly intriguing subgroup consisted of patients with both HER2+/AR+ status ($n = 50$) with available previous treatment data. This subgroup was divided into those initially treated with ADT ($n = 41$) and those with anti-HER2 therapy as first-line treatment ($n = 9$). Among those who continued with ADT after initial progression, the ORR was 30% ($n = 39$), while among the nine patients re-exposed to anti-HER2 therapy, five responded (55.5%), with two achieving complete responses. Notably, both patients who switched from ADT to anti-HER2 therapy exhibited partial responses (see Figure 3B).

Table 1. Principal cohort characteristics

Variable	Ductal carcinoma, $N = 219$[a]	ACC, $N = 167$[a]	Adenocarcinoma NOS, $N = 23$[a]	Mucoepidermoid, $N = 17$[a]	*P*-value[b]
Median age at diagnostic (years)	61 (54-66)	53 (45-62)	59 (52-68)	59 (53-70)	<0.001
Sex					
Female	28 (12.7)	81 (50)	5 (22)	2 (12)	
Male	179 (81.7)	68 (42)	18 (78)	15 (88)	
No data	12 (5.5)	12 (7.5)	0 (0)	0 (0)	
Primary site					
Parotid	116 (53)	44 (27)	8 (35)	8 (47)	
Submandibular	29 (13)	16 (9.9)	1 (4.3)	1 (5.9)	
Minor glands	13 (5.9)	57 (35)	2 (8.7)	2 (12)	
No data	61 (28)	44 (27)	12 (52)	6 (35)	
Distant metastasis					
Yes	139 (63)	74 (44)	12 (52)	10 (59)	
No	67 (31)	39 (23)	11 (48)	7 (41)	
No data	13 (5.9)	54 (32)	0 (0)	0 (0)	
Previous systemic treatment					0.005
Yes	106 (48)	97 (58)	17 (74)	8 (47)	
No	100 (46)	70 (42)	6 (26)	9 (53)	
No data	13 (5.9)	0 (0)	0 (0)	0 (0)	

ACC, adenoid cystic carcinoma; NOS, not otherwise specified.
[a]Median (interquartile range); *n* (%).
[b]Kruskal−Wallis rank sum test; Fisher's exact test.

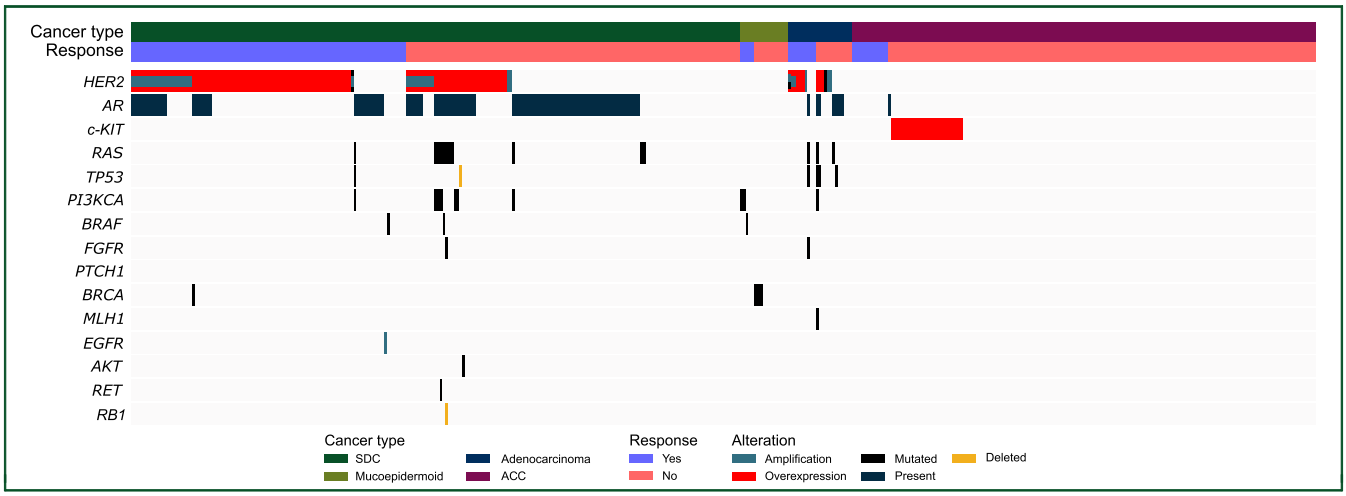

Figure 2. Oncoprint displaying molecular features reported by authors for the entire cohort ($n = 426$). Cases are arranged by histology and response to the treatment of interest.
ACC, adenoid cyst carcinoma; SDC, salivary duct carcinoma.

The utilization of other treatment modalities for SDC was limited, with minimal reported responses. Platinum-based protocols, either alone or in combination with taxanes, showed responses in only one out of seven patients. Out of 33 SDC cases treated with immunotherapy (e.g. nivolumab, pembrolizumab), six exhibited confirmed responses, without any added value observed with the addition of ipilimumab. Finally, the subset of patients treated with TKIs was small ($n = 7$), with three responses observed with afatinib, vemurafenib, and tipifarnib.

The second largest group included in the study was ACC ($n = 167$), where chemotherapy was utilized in 44 cases, primarily based on platinum agents alone or in combination with doxorubicin or 5-fluorouracil. Notably, schemes incorporating doxorubicin demonstrated more responses ($n = 6/21$) compared with cisplatin alone ($n = 2/23$), although this difference was not statistically significant (Fisher's exact test $P = 0.125$).

Following chemotherapy, TKIs were the most frequently employed treatment of ACC ($n = 89$). These included a range of multitarget agents: axitinib, imatinib, lenvatinib, nintedanib, sorafenib, and sunitinib. Despite the overexpression of *KIT* in all patients treated with imatinib plus cisplatin, no response was reported. Among TKIs, only two responses were observed in ACC patients: one with axitinib ($n = 1/6$) and one with sorafenib ($n = 1/16$).

Immunotherapy was indicated in 33 ACC patients, primarily limited to the use of nivolumab plus ipilimumab, showing three partial responses.

In the minor groups, notable responses to treatment were observed, particularly with targeted agents. In cases of mucoepidermoid carcinoma, two patients with rare $BRAF^{V600E}$ and $PTCH\text{-}1^{Q400*}$ mutations rapidly responded to vemurafenib and vismodegib, respectively. Adenocarcinomas NOS displayed sensitivity to *HER2* inhibition, with patients responding to trastuzumab ($n = 2/11$) or trastuzumab plus pertuzumab ($n = 5/11$). Other treatments, such as combined chemotherapy and abiraterone, also showed responses in a few cases.

Studying overall survival is challenging when we include salivary gland cancers with different histology and recurrent or initially metastatic disease. For a better understanding of

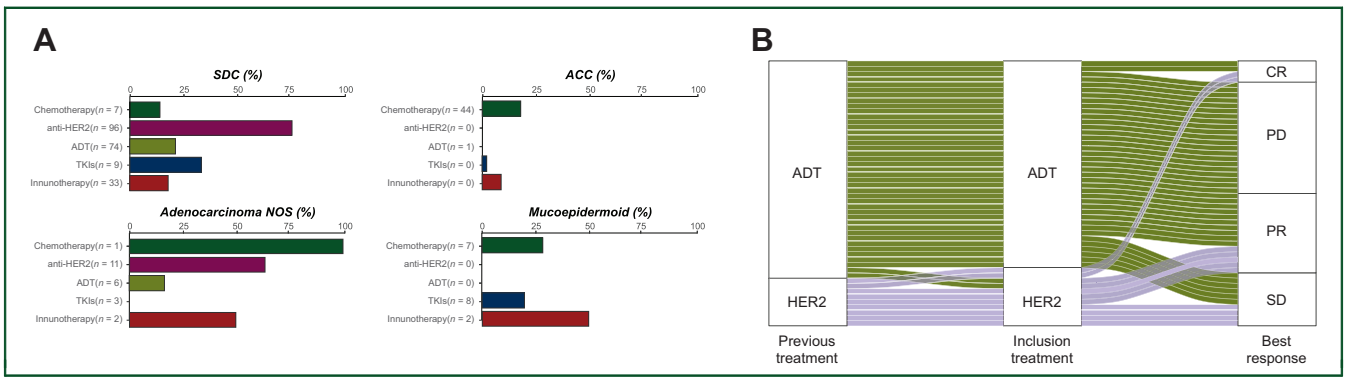

Figure 3. Response to treatment in salivary gland cancers. (A) Proportions of responders among the total number of treated patients, by cancer type. No statistical differences were found (Fisher's exact test $P > 0.05$) and are not represented. (B) Alluvial plot showing the best response for the treatment of interest in a subset of patients HER2+/AR+ ($n = 50$) with previous treatment data available.
ACC, adenoid cyst carcinoma; ADT, androgen deprivation therapy; AR, androgen receptor; CR, complete response; HER2, human epidermal growth factor receptor 2; NOS, not otherwise specified; PD, progressive disease; PR, partial response; SD, stable disease; SDC, salivary duct carcinoma.

the effect of systemic treatments in overall survival, we selected 187 cases without prior systemic interventions to evaluate the impact of response in the outcome. There was a benefit for patients with partial or complete response exhibiting significantly prolonged median overall survival compared with those with stable or progressive disease at first line (responders 38 versus non-responders 18.7 median months, Cox's regression hazard ratio (HR) 2.25; 95% CI 1.37-3.70; $P < 0.001$) (Figure 4A). The analysis of overall survival based on histology is even more difficult due to numerous variables involved inter- and intra-cancer types. Nevertheless, we could describe overall survival benefit at first-line treatment for anti-HER2 agents over ADT in SDC cases (36 versus 11.7 months, Cox's regression HR 0.21; CI 0.11-0.39; $P < 0.001$) (Figure 4B). Then we analyzed the impact in overall survival for treatment-naive ACC with a benefit for those under chemotherapy (combined or alone) versus any type of TKI (overall survival median 48 versus 18.7 months, Cox's regression HR 3.34; CI 1.44-7.73; $P < 0.005$) (Figure 4C).

DISCUSSION

In this study, we conducted a comprehensive systematic review involving 44 studies and comprising 426 cases diagnosed with salivary gland cancer who underwent systemic therapy due to advanced or relapsed disease. The analysis of this diverse cohort, including variations in histology, molecular features, and treatments administered, revealed significant heterogeneity in clinical presentation and treatment outcomes. Importantly, our findings highlight the pivotal role of systemic treatment response as a positive determinant of survival.

Recent research endeavors have underscored the significance of overexpression for *HER2* and AR in SDC and adenocarcinoma NOS within this intricate landscape. These receptors have captivated the scientific community due to their strong associations, where *HER2* amplification or positivity on immunohistochemistry is a negative prognostic factor, but at the same time a predictive factor of favorable responses to targeted treatments.[73,74] The recent results from a trastuzumab deruxtecan (T-DXd) pan-tumor phase II trial, published after our papers search, enhance the importance of *HER2* expression levels (3+) impact on response, PFS, and overall survival.[75] Despite salivary cancer patients ($n = 19$) being combined with other cancer types, the fact that one-third of patients from this group objectively reduced tumor size makes T-DXd an option after progression to chemotherapy or other anti-HER2 agents. Also, the simultaneous expression of AR and *HER2* within a subset of patients with salivary gland cancer presents a compelling scenario, especially due to the disease aggressiveness.[10] In our cohort, the administration of anti-HER2 therapies yielded significantly elevated objective response rates (55.5%), albeit based on a relatively constrained number of HER2+/AR+ cases ($n = 13$). While our study did not encompass a comprehensive analysis of the transition between ADT and anti-HER2 treatment, a recent study by Kawakita et al.,[76] conducted on a larger SDC cohort, echoed similar findings, reinforcing the benefit of first-line anti-HER2 treatment in this context.

In stark contrast, a notable subset of patients within our cohort lacked discernible molecular drivers, with ACC emerging as the predominant subgroup in this category. As known, ACC confirmed its distinctive biology characterized by the lowest response rates to treatments among all evaluated histological subtypes. ACC showcased significantly extended survival durations, however, even in the presence of metastatic disease. This has been associated with females, disease-free survival, lung metastasis, and the absence of liver and bone metastasis[77] making surveillance strategy a reasonable option for these patients. Of note, when we evaluated systemic treatments for ACC, chemotherapy was a superior option in terms of survival outcomes only compared with the included TKIs.[78] It is important to remark, however, that certain studies with relevant results could not be included in our analysis due to our predefined criteria and deserve mention. Studies including sorafenib, axitinib or rivoceranib[22,79-81] have demonstrated responses, and they are currently a recommended option for ACC patients with progressive or symptomatic disease.[16,17] Despite our series including a lenvatinib paper with an independent evaluation committee showing no objective responses,[68] the use of this *VEGFR* inhibitor has demonstrated considerable median disease control rate in prospective studies.[82] Additionally, *NOTCH1* mutations are usually related to initially metastatic disease and more aggressive behavior with reduced overall survival in ACC patients.[78,83-85] AL101 is a gamma-secretase inhibitor, a key enzyme for NOTCH activation receptors which are under

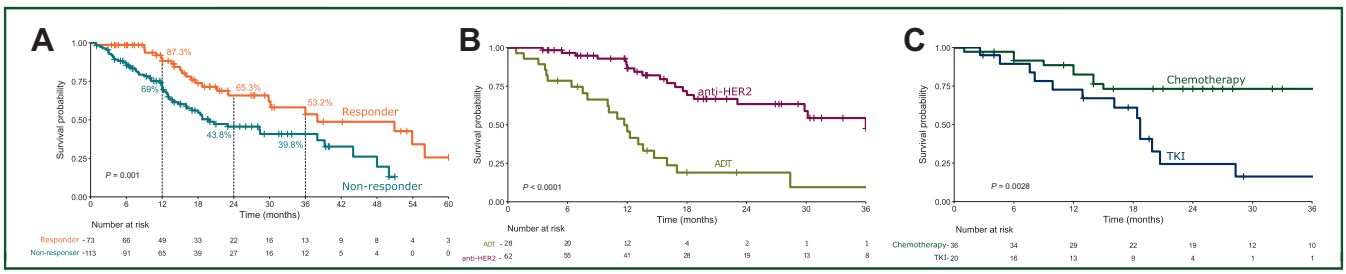

Figure 4. Overall survival analysis for patients without previous systemic treatment in recurrent/metastatic disease, *P*-value was calculated with log-rank test. (A) Effect of response to treatment on survival for patients without previous systemic treatment ($n = 187$) at 12, 24, and 36 months. (B) Comparison of survival for anti-HER2 therapy versus androgen deprivation therapy (ADT) in salivary duct carcinoma cases without previous treatment ($n = 90$). (C) Comparison of survival in adenoid cystic carcinoma (ACC) cases without previous treatment ($n = 56$) treated with any tyrosine kinase inhibitor (TKI) versus any chemotherapy.
HER2, human epidermal growth factor receptor 2.

analysis (www.clinicaltrails.gov: NCT03691207 and NCT04973683).[86] Then, the *MYB-NFIB* fusion gene is present in a substantial proportion of ACC (30%), promoting tumor cell proliferation and survival,[87,88] with REM-422 being currently under evaluation as an inhibitor (NCT06118086).

The advent of next-generation sequencing techniques has ushered in new prospects for the treatment of salivary gland cancer patients harboring infrequent mutated drivers, allowing for the inclusion of few patients in basket trials with high sensitivity such as those involving vemurafenib and vismodegib. As we shift towards a comprehensive analysis of established targets within tumor samples, it becomes imperative to explore novel therapeutic avenues always after clearly defining the correct pathologic diagnosis by expert pathologists. Conversely, multitarget inhibitors (e.g. sunitinib, gefitinib, nintedanib, etc.) have shown limited response rates, needing further exploration, possibly in conjunction with more efficacious treatments.

The use of immunotherapy in salivary gland cancer did not demonstrate significant responses. The microenvironment of ACC characterized by the presence of immune suppressor cells such as tumor-associated macrophages and myeloid-derived suppressor cells, low or null programmed death-ligand 1 (PD-L1) or cytotoxic T-lymphocyte associated protein 4 (CTLA-4) receptors and low CD8+ infiltrating lymphocytes.[89,90] A similar situation was described for SDC, where reduced expression of major histocompatibility complex 1 (MHC-1) appears to be directly related to the presence of immunosuppressive macrophages.[91] Notably, patients who exhibited a positive response have often been associated with high-grade histology, factors like neoantigen production or PD-L1 expression, and high T-cell receptor (TCR) clonality,[67] mirroring patterns observed in other cancers that respond favorably to immunotherapy.[92] Because of this, to date the use of immunotherapy should be restricted to patients with high tumor mutational burden (TMB) and/or high microsatellite instability (MSI-H).[17]

Acknowledging the inherent limitations in our study, stemming primarily from its retrospective nature and associated design constraints, is crucial. To reduce data variability and risk of bias, our criteria for paper selection were strict and applied from the beginning of our research. This is reflected in the exclusion of prospective studies to obtain comparable results following a systematic selection, although we were able to include most of the treatments mentioned in practice guidelines. An important aspect, such as disease control during treatment, was not considered during this review due to its difficulty in retrospective analysis, but it must be acknowledged as an essential factor to consider. To mitigate these challenges, we focused on key objective parameters such as tumor response and overall survival.

Conclusion

The utilization of systemic treatments demonstrates a beneficial impact on overall survival in relapsed or newly advanced salivary cancers, with response rates varying among treatments and histological subtypes. The efficacy of targeted therapies significantly influences this benefit, emphasizing the importance of personalized therapeutic strategies to optimize outcomes for patients.

ACKNOWLEDGEMENTS

We would like to thank Drs Yuichiro Tada, Cristina Rodriguez, Lillian Siu, John Hainsworth, and Carla van Herpen for generously responding to our inquiries, which contributed to this paper.

FUNDING

This work was supported by Fondation Nelia et Amadeo Barletta (no grant number) (to DP and SI).

DISCLOSURE

LL declares the following conflicts of interest: research funds donated directly to the institute for clinical trials from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Celgene International, Eisai, Exelixis, Debiopharm International SA, Hoffmann-La Roche Ltd, IRX Therapeutics, Medpace, Merck-Serono, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Roche, and Buran; occasional fees for participation as a speaker at conferences/congresses or as a scientific consultant for advisory boards from AstraZeneca, Bayer, MSD, Merck-Serono, AccMed, Neutron Therapeutics, Inc., and Alentis.

SC declares the following conflict of interest: occasional fee for participation as a congress speaker from AccMed.

All other authors have declared no conflicts of interest.

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