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Review

HER2-targeted therapies for salivary gland cancers

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ABSTRACT

Salivary gland cancers (SGCs) are a heterogeneous group of rare tumors including various histological subtypes with different molecular profiling. Human epidermal growth factor receptor 2 (HER2) is one of the most intriguing and studied molecular alterations with prognostic and predictive roles. Indeed, HER2 overexpression is commonly correlated with aggressive histological subtypes and poorer prognosis. However, HER2 may represent the target of personalized treatment.

We performed a literature review of use of anti-HER2 targeted agents for treatment of recurrent or metastatic SGCs. The efficacy and safety of anti-HER2 were firstly evaluated in patients affected with other solid tumors, mostly breast and gastric cancers. For SGCs the literature is mainly comprised of case reports or case series and small clinical trials. The most common used drug is trastuzumab in combination with chemotherapy (i.e. taxanes, capecitabine, carboplatin, eribulin) or with another anti-HER2 targeted agent (i.e. pertuzumab). The use of anti-HER2 therapies induces improvement in clinical responses, which are mostly durable. Besides, new anti-HER2 drugs such as antibody-drug conjugates (ADC) (i.e. trastuzumab emtansine, trastuzumab deruxtecan) have been introduced in this setting inducing further therapeutic advances.

Anti-HER2 treatment strategy is emerging as potentially effective in selected HER2 overexpressing SGCs. However, prospective and multicentric clinical trials are needed to evaluate the efficacy of these therapeutic regimens within larger cohorts and to assess the most appropriate treatment sequence strategy.

Introduction

Salivary gland cancers (SGCs) are rare tumors accounting for <5% of head and neck cancer [1] and represent a widely heterogeneous group of histological malignancies with more than 20 histotypes included in the last World Health Organization (WHO) classification.[2]

The most common histotype of major SGCs is mucoepidermoid carcinoma (MEC), representing around a third of SGCs cases, followed by adenoid cystic carcinoma (ACC) with 23.8 % of cases [3]. The pathological diagnosis is challenging due to the wide heterogeneity of histological subtypes and the overlapping of morphological patterns. Correlation of molecular profiling is needed to accurately distinguish some histologies and to identify potential biomarkers able to tailor treatment and to predict response. Of note, the translocation t (12;15) (p13; q25) leading to gene fusion ETV6-NTRK3 is pathognomonic for secretory carcinoma, NOS [4] and the gene fusion CRTC1-MAML2/ CRTC3-MAML2 mainly occur in low and intermediate-grade MEC [56]. Moreover, the MYB-NFIB fusions is a typical genomic alteration in

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ACC [7–9].

Recently, European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines provided recommendations for SGCs' management based on published literature and expert panel consensus [10,11]. However, some points have a low or medium strength of recommendation, due to lack of data in literature, deserving more in depth and specific study and how to implement it in clinical practice.

Multiple targets potentially useful for a tailored approach have been identified in the last few years. Androgen receptor (AR) and human epidermal growth factor receptor 2 (HER2) are the most investigated targets.

AR expression differ among various subtypes of SGCs, being mostly represented in salivary duct carcinoma (SDC) (in the latter, the prevalence in different studies ranges from 43% to 100%). In other subtypes of SGCs, AR positivity is detected at lower rates: in adenocarcinoma not otherwise specified (A-NOS) and acinic cell carcinoma, it is reported in 26% and 15%, respectively. [12]The prognostic role of AR expression in SDC is challenging to evaluate, due to the disease rarity and the low number of AR-negative cases. In some studies, it is reported a trend of better disease free survival (DFS) in AR-positive compared to AR-negative SDC patients, but this association has not been recognized by other SGCs subgroups. [13,14]

In 25–30% of cases, AR and HER2 could be simultaneously expressed in the same tumor. [34] Co-expression of AR and HER2 is scarced reported in literature. Can et al. found combined HER2 and AR overexpression in 22 out to 132 carcinomas: 14 SDC, three poorly differentiated carcinomas NOS, two oncocytic carcinomas, one squamous cell carcinoma, one high grade carcinoma ex pleomorphic adenoma, and one intraductal carcinoma. [15] A recent sudy, focused on AR-positive SDC, found a higher risk of CNS metastasis in HER2-positive compared to HER2-negative cohort. [16]

Currently, a randomized phase II European Organisation for Research and Treatment of Cancer (EORTC) trial (NCT01969578) is evaluating the efficacy and safety of androgen deprivation therapy (experimental arm) vs chemotherapy (standard arm) in patients with recurrent/metastatic, AR overexpressing [defined as immunohistochemistry (IHC) staining in $\geq$ 70 % of tumor cells], advanced SGCs.

The expression of HER2 in SGCs is heterogeneous among histological subtypes: typically, it is restricted to SDC (up to 30%) and A-NOS (up to 21%), two entities that represent high grade carcinomas according to histopathological classification [17–19], followed by MEC [20,21].

In case of HER2 overexpressed disease, positive results with anti HER2 therapy are mainly restricted in the setting of recurrent/metastatic disease; however, in some retrospective studies a role for adjuvant anti HER2 therapy is emerging. [22]

In this review, we provide an overview of the current literature regarding HER2 targeted therapies in advanced SGCs with some insights on the possible role of new drugs and development of future research in an earlier setting.

Standard of care for localized and advanced SGCs

SGCs are associated with high rates of locoregional and distant recurrence (50–60 %) [23,24] with a median time of 16 months until occurrence of distant metastases [25]. Five-year overall survival (OS) rate is ranging between 11.5% and 44%, [23,24] and a median overall survival of 48–79 months after diagnosis [21,26].

The standard treatment for SGCs consists of surgical resection with or without adjuvant radiotherapy.

There is no proof of a beneficial effect of adding chemotherapy to post-operative radiotherapy [10]. All patients with recurrent SGCs should be evaluated within a multidisciplinary setting. Unresectable locoregional recurrence or metastatic disease may be treated with definitive radiotherapy or systemic chemotherapy in a palliative setting, respectively. Because of rarity of disease and lack of prospective studies, there are no standard or evidence-based chemotherapeutic recommendations, especially in the curative setting. In the recurrent/metastatic disease, various regimens of single agent or combination chemotherapy have been tested in small sample size studies with a 15–50% response rate for a duration of response of 6–9 months [23,24]. The most active single agents include cisplatin, cyclophosphamide, doxorubicin and 5-fluorouracil [25,26].

Therefore, more effective treatment approaches are eagerly awaited. Particularly, SDC and ductal carcinoma of the breast share morphological and immunophenotypical similarities, as both are infiltrating ductal carcinomas with elements of comedonecrosis and a reactive desmoplastic stroma. Furthermore, these tumors may exhibit HER2 overexpression and gene amplification [21,25,27,28]. Because of these similarities, it was proposed that HER2-targeted therapies could potentially be of benefit in HER2-positive SGCs. Trastuzumab is the first introduced recombinant humanized monoclonal antibody that binds the extracellular domain of HER2 with high affinity and thus inhibits proliferation of tumor cells overexpressing HER2.

HER2 overexpression and its putative role in SGCs

The HER2 proto-oncogene, which encodes a membrane receptor protein of the epidermal growth factor receptor family, is overexpressed in a variety of epithelial malignancies [29]. HER2-activated protein forms heterodimers on the cell surface, which propagates activation of the PI3K and RAS pathways and affects proliferation, survival and angiogenesis [30]. HER2 is known as a metastasis- promoting factor. HER2 (also known as ERBB2) oncoprotein is involved in matrix degradation, proteolitic activity, and increases in vessel permeability, endothelial cell growth, proliferation, migration, and differentiation.

The most studied expression of HER2 is in SDC, consistently with its similarities with ductal breast carcinoma; HER2 gene amplification determined by FISH is found in 20% to 30% of SDC [14,27,50–52].

A recent metanalysis [53] found 6 subtypes of malignant SGCs with positive HER2 rates higher than 20%: SDC in situ, SDC, carcinoma ex pleomorphic adenoma, poorly differentiated adenocarcinoma, adenocarcinomas NOS, squamous cell carcinomas and MEC.

Futhermore Cavalieri et al. [16] found an overexpression of HER2 in 42% of 74 AR positive SGCs, regardless of histotype.

HER2 overexpression is associated with worse outcome in SDC and AR-positive SGCs with higher risk of recurrence [16,31,32]. By contrast, it seems to be not so clear for adenocarcinoma NOS [33].

The overexpression of HER2 is tipically associated with more aggressive tumors and poor prognosis [34,35]. With conventional chemotherapy, HER2-positive SDC has a high incidence of recurrence and a rapid disease progression [36–38].

In MEC, Press et al. found that ERBB2 immunostaining was a prognostic marker of poor clinical outcome, regardless of tumour site, size, grade and lymph node status [14].

Also in the study by Jaehne et al. [39] moderate (17.7% of patients) and strong staining (20.6% of patients) for ERBB2were associated with worse OS and higher rate of distant metastasis. Other authors have also found that ERBB2 overexpression is an indicator of aggressiveness and poor prognosis [37,40].

In 2019, Santana T et al. [32] observed that apocrine HER2 subtype (AR+/HER2 +) of SGCs was significantly associated with lower OS. In fact, median OS for apocrine A (AR+/HER2−/MIB1- low) cases was 48 months, for apocrine B (AR+/HER2−/MIB1-high) cases 60.13 months and for apocrine HER2 cases 30.56 months.

Conversely, in other studies such association was not found, in fact HER2 positivity did not impact DFS or OS among patients with SGCs [32,33,41–43]. All these findings together confirm the importance of assessing the HER2 status at diagnosis of SDC and adenocarcinoma NOS at least, which is largely missing at present in clinical practice.

Diagnostic methods of her2 molecular alterations

HER2 is a member of the epidermal growth factor receptor family and its overexpression is widely recognized to play a critical role in initiation and maintenance of several malignancies [44].

Because studies validating HER2 scoring systems in SGCs are lacking, the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) suggest to assess HER2 status with a combination of immunohistochemistry (IHC) and in situ hybridization (ISH) and interpreted using the guidelines for HER2 in breast cancer [45,46].

The next-generation sequencing (NGS) technologies, recently employed to identify molecular therapeutic targets, commonly allow for concurrent detection of copy number alterations (CNA) and can be seen as an alternative to multiple single-gene tests [47].

NGS has been already validated in large set of breast and gastroesophageal carcinomas [48] was also recently applied by Ferguson et al. in a cohort of 67 SDC [49].

Published data

The current clinical literature review of use of anti-HER2 targeted agents for treatment of locally advanced and recurrent/metastatic SGCs is summarized in Table 1. The literature largely comprises case reports/series and some phase 2 studies, mainly in recurrent or metastatic setting. Combinations of trastuzumab and chemotherapy are mainly derivate from the commonly used treatments in HER2 overexpressing breast and gastric cancers. Taxanes, including docetaxel and paclitaxel, are the most frequently used chemotherapeutic drugs. Other cytotoxic drugs combined with trastuzumab are carboplatin or capecitabine. Trastuzumab is firstly administered in combination with standard chemotherapy followed by a maintenance therapy with trastuzumab alone. In many cases of advanced HER2 positive SGCs, a long lasting overall response rate has been obtained with these therapeutic combination strategy (Table 1).

The major limitations of these reports are the retrospective nature, the heterogeneous chemotherapy protocols and the small sample size [55]. Due to the rarity of SGCs, randomized clinical trials are lacking. These results underscore the need for the assessment of trastuzumab or trastuzumab plus taxanes in a prospective study. Haddad et al. reported the results of a prospective, phase II trial. Fourteen patients were enrolled and treated with trastuzumab as single agent. Unfortunately, the study was closed prematurely because of the low frequency of HER2-overexpressing SGCs (17%) [25]. Partial response and stable disease were demonstrated in only 1 and 2 patients, respectively, whereas the others experienced progression of disease with a median time of 4.2 months. The analysis of this trial shows two main limitations: the difficult accrual typical for rare tumors and the lack of gene amplification status to define HER2 status [56].

The response to trastuzumab may be dependent on HER2 overexpression and gene amplification.

In 2019, Takahashi et al. reported an ORR of 70.2%, a median progression free survival (PFS) and OS were of 8.9 months and 39.7 months, respectively [57] in patients treated with trastuzumab plus docetaxel in 57 metastatic, previously treated, HER2-overexpressing SDC patients.

Recently, many others HER2 targeting agents have been introduced in the current treatment of breast cancer and studied also in HER2 positive SGCs.

Lapatinib is a dual inhibitor of the tyrosine kinase domains of the epidermal growth factor receptor (EGFR) and HER2. Lapatinib at 1,500 mg daily dose has demonstrated preliminary antitumor activity in a phase II study in which 15 out of 19 ACC patients and in 8 out of 17 non-ACC patients, with expression of 1 + o 2 + HER2, achieved stable disease of at least 6 months, although no objective responses were observed [58]. However, this study did not assess gene amplification status and included a large variety of SGCs subtypes.

In addition, trastuzumab emtansine (T-DM1) is a monoclonal antibody-cytotoxic drug conjugate combining trastuzumab with emtansine, a microtubule inhibitor. Correa et al. started T-DM1 treatment for a HER2 3 + SDC patient with progressive disease during trastuzumab maintenance obtaining a partial response in the neck skin, liver and bone lesions with a 1-year duration of response. For further progressive disease at the bones and neck sites this patient was treated with combination of vinorelbine with trastuzumab plus pertuzumab, with response lasting 4 months [29].

In this context, MyPathway, a phase II clinical trial showed promising efficacy in the subgroup of 15 patients with HER2-positive SGCs (SDC, adenocarcinoma NOS, MEC histologies) treated with the combination of pertuzumab with trastuzumab (without chemotherapy). Overall response rate was 60 % (8 PR, 1 CR) with durable responses. Median OS was 20.4 months [59].

These case reports also highlight the need to improve our knowledge on the best sequences and/or combinations of such therapies [29,59,60].

Neratinib is a newer potent, oral, irreversible inhibitor of the ErbB family of receptor tyrosine kinases. It has been used in patient treated with multiple lines of antiHER2 directed therapy obtaining disease control [61].

Treatment sequencing strategies of anti-her2 agents

Sousa et al. presented retrospective data collected from patients affected with SDC or adenocarcinoma NOS treated at The University of Texas MD Anderson Cancer Center between 1990 and 2020. Tumors were classified as HER2-positive if they scored as 2 + or 3 + by IHC, regardless of FISH results. Seventeen patients with HER2 positive recurrent or metastatic disease received at least 1 regimen containing anti HER2 agent, 10 patients as first-line therapy, with ORR of 50%. The mPFS was higher in patients who received a HER2 inhibitor as part of first-line therapy than in patients who received chemotherapy alone as first-line therapy (11.0 vs. 5.6 months; hazard ratio [HR], 0.84; P =.7). Seven patients were re-challenged with HER2 inhibitors; the ORR and median PFS for second line therapy were 29% and 6.7 months, respectively [76].

Uijen et al. reported a case series of 13 SDC patients treated with trastuzumab/pertuzumab plus docetaxel with ORR of 58%. Median OS was 42.0 months. Median PFS was 6.9 months. Seven patients received T-DM1 for progressive disease with ORR of 57% and PFS of 4.4 months [79].

Hence, the HER2 blockade seems to be beneficial to long term responses.

Some phase II trials, case series, and case reports have demonstrated benefits for patients treated with combined chemotherapy and trastuzumab in recurrent or metastatic setting. After progression, there is no standard treatment for patients with HER2-positive metastatic SDC.

Ongoing clinical trials

Novel antiHER2 drugs and their combinations with other agents or chemotherapy for HER2 positive SGCs are under evaluation to improve survival outcomes. Targeted therapies with tyrosin kinase inhibitors (TKIs) or monoclonal antibodies (mAbs) alone often show inadequate efficacy, due to their low cytotoxicity and poor penetrance into tumors [84]. ADCs represent a new and promising class of anticancer therapeutic strategy. Typically, an ADC is a combination of a target-specific mAb linked to a cytotoxic drug with a chemically synthetic linker. The mAb components of ADCs bind to the specific antigen on the surface of cancer cells, leading to the internalizations of ADCs [85].

T-DM1 is the first ADC approved composed of trastuzumab and a microtubule-depolymerizing maytansinoid derivative, DM1 [84].

Trastuzumab deruxtecan (T-Dxd) is the second approved HER2-targeting ADCs. The components of T-Dxd are trastuzumab and a topoisomerase I inhibitor DXd, which is a novel water-soluble derivative

Table 1
Clinical studies evaluating HER2- targeted therapies in SGCs (advanced and adjuvant settings).

Author, Year	Study design	number of patients	gender	mean age (age range)	hystology	HER2 status	IHC; FISH, NGS	setting	treatment	response	Survival outcomes	reference
Iqbal, 2014	case report	1	M	59	poorly differentiated ductal adenocarcinoma	3+	IHC/FISH	I line	trastuzumab + docetaxel		PFS 8 months, OS 5 years	[24]
Haddad, 2003	phase II	14	10M, 4F	60 (44–80)	mucoepidermoid carcinoma (3), adenoid cystic carcinoma (2), adenocarcinoma (7), squamous cell carcinoma (2)	2+, 3+	IHC	I line	trastuzumab	1/14 PR (>1 year), 2/14 SD	mTTP 4.2 monhs, 2 patients with SDC had stable disease for 24 and 42 weeks	[25]
Limaye, 2013	retrospective case series	5	NA	64 (51–82)	SDC	3+	IHC/FISH	I line	trastuzumab + carboplatin/ paclitaxel	1/5 CR, 2/5 PR, mDOR 18 months (range: 8–52 months)	mOS 40 months	[54]
Kadowaki, 2013	case report	1	M	74	carcinoma ex pleomorphic adenoma	3+	IHC/FISH	I line	trastuzumab + paclitaxel	CR	PFS > 13 months	[62]
Firwana, 2012	case report	1	M	62	adenocarcinoma	3+	IHC	I line	trastuzumab + paclitaxel	CR, DOR > 1 year		[63]
Nashed and Casasola, 2009	case report	1	M	49	SDC	3+	IHC	II line	trastuzumab + docetaxel	PR, DOR > 20 months		[64]
Prat, 2008	case report	1	M	62	SDC	positive	IHC/FISH	I line	trastuzumab + carboplatin/ paclitaxel	CR	PFS > 14 months	[26]
Sharon, 2010	case report	1	M	58	carcinoma ex pleomorphic adenoma	3+	ICH/FISH	I line	trastuzumab + capecitabine	CR, DOR > 2 years		[65]
Kaidar-Person, 2012	case report	1	M	64	SDC	3+	IHC	I line	trastuzumab + carboplatin/ paclitaxel	CR, DOR > 1 year		[28]
Locati, 2005	case series	4	NA	NA	salivary gland carcinoma	3+	IHC/FISH	I line (3), II line (1)	not specified	1/4 SD	mPFS 2.5 months	[66]
Gibo, 2019	case report	2	M	59, 68	SDC	3+/amp vs non amp	IHC/FISH	II line	trastuzumab + paclitaxel	1 CR, 1 PD, DOR > 2 years		[67]
Ghazali, 2016	case report	1	M	68	AD-NOS	3+	IHC	I line	trastuzumab	CR	OS > 3 years	[68]
De Block, 2016	case series	6	M	NA (54–69)	mucoepidermoid carcinoma (2), salivary duct carcinoma (3), acinar cell carcinoma (1)	2 + e 3+	IHC/FISH	I or II line	trastuzumab + paclitaxel/ docetaxel	5 PR, 1 SD	mPFS 10 months for 4 patients which disease has progressed	[56]
Thorpe, 2016	case series	2	M	35–72	carcinoma ex pleomorphic adenoma, SDC	3+	IHC/FISH/ genome profiling	II/I line	trastuzumab + paclitaxel/ (carboplatin)	1 PR, 1 CR, mDOR 14 months		[69]
Correa, 2018	case report	1	M	79	SDC	3+	IHC	III/IV line	ado-trastuzumab emtansine, vinorelbin + trastuzumab/ pertuzumab	PR, DOR > 1 year		[29]
van Boxtel, 2017	case series	2	M/F	63/48	SDC	3+	IHC/FISH	I line	trastuzumab + pertuzumab docetaxel, T-DM1	PR/SD, DOR > 17 months/8 months		[60]
Sorenson, 2017	case report	1	M	31	SDC	3+	IHC/FISH	M	trastuzumab, trastuzumab + lapatinib, lapatinib + capecitabine, T-DM1, neratinib	CR, DOR 3 years		[61]

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Table 1 (*continued*)

Author, Year	Study design	number of patients	gender	mean age (age range)	hystology	HER2 status	IHC; FISH, NGS	setting	treatment	response	Survival outcomes	reference
Algunik, 2007	phase II	36 (19 ACC; 17 non-ACC)	28M, 11F	52 ACC (38–72), 64 non-ACC (45–80)	ACC and non ACC	1+,2+,3+	IHC	R/M	lapatinib	15/19 SD, 8/17 SD		[58]
Kurzrock, 2020	phase II basket	15	12M, 3F	NA (37–80)	salivary duct adenocarcinoma, adenocarcinoma unspecified carcinoma, mucoepidermoid carcinoma, invasive ductal carcinoma	3+	IHC/FISH/NGS	I-IV line	trastuzumab + pertuzumab	ORR 63 % (8 PR, 1 CR)	mPFS 8.6 months, mOS 20.4 months	[59]
Takahashi, 2019	phase II	57	51M, 6F	57 (38–82)	SDC	2+, 3+	IHC/FISH/HER2 gene copy number	M	trastuzumab + docetaxel	ORR 70.2 % (8 CR, 32 PR)	mPFS 8.9 months, mOS 39.7 months	[57]
Perissinotti, 2013	case series	13	9M, 4F	58 (28–67)	SDC	2 + amplified, 3+	IHC/ISH	M	trastuzumab or trastuzumab + chemotherapy (vinorelbine, carboplatin and paclitaxel, docetaxel, paclitaxel, carboplatin and docetaxel, bavacizumab and lapatinib)	3 PR, DOR 3–8 months		[55]
Nabili, 2007	case report	3	F	68 (55–69)	SDC	3+	IHC/FISH	R	trastuzumab + paclitaxel/carboplatin	1 CR (DOR 36 months), 1 PR (DOR 19 months), 1?		[36]
Lee, 2014	case report	1	F	77	SDC	3+	IHC/FISH	I line	trastuzumab	CR, DOR > 18 months		[70]
Krishnamurthy, 2013	case report	1	M	72	SDC	3+	IHC	I line	trastuzumab + docetaxel	PR, DOR > 2 years		[71]
Falchook, 2014	case report	1	M	55	SDC	3+	IHC/FISH	M	trastuzumab + docetaxel/carboplatin, trastuzumab + paclitaxel, trastuzumab + lapatinib + bevacizumab	PR, PR, CR		[72]
Longo, 2020	case report	1	M	53	SDC	positive	IHC	M	trastuzumab + pertuzumab + weekly carboplatin/paclitaxel	PR		[73]
Li, 2019	phase II basket	10	9M, 1F	65 (36–90)	SGC	3+	IHC/FISH/NGS/FLIM-FRET	M	T-DM1	ORR 90 %		[74]
Lee, 2022	phase II	43	86 % M, 14 % F	60 (35–81)	SDC (84 %), adenocarcinoma (9 %), high grade mucoepidermoid carcinoma (2 %), other subtype (5 %)	2 +, 3+	IHC/FISH	M	herzuma + docetaxel anhydrous (Nanoxel)	ORR 67 %, 29 PR	mPFS 8.2 months, mOS 23.3 months	[75]
Sousa, 2022	retrospective	17	NA	NA	SDC or adeno-NOS	2+, 3+	IHC/FISH	M	trastuzumab + chemotherapy	ORR 47 %	mPFS 9.6 months	[76]
Taha and Billan, 2021	case report	1	M	85	SDC	3+	IHC	R	trastuzumab + carboplatin/paclitaxel, T-DM1	CR (DOR > 4 years), CR		[77]

(*continued on next page*)

Table 1 (*continued*)

Author, Year	Study design	number of patients	gender	mean age (age range)	hystology	HER2 status	IHC; FISH, NGS	setting	treatment	response	Survival outcomes	reference
										(DOR > 6 months)		
Ma, 2022	case report	1	M	78	SDC	3+	IHC/FISH	M	trastuzumab + cisplatin + capecitabine/trastuzumab + pembrolizumab	PR (DOR > 6 months)		[78]
Uijen, 2022	case series	13	10M, 3F	61 (48–75)	SDC	2+, 3+	IHC/FISH	R/M	trastuzumab + pertuzumab + docetaxel, T-DM1	ORR 58 %, ORR 57 %	mPFS 6.9 months, mOS 42 months/ mPFS 4.4 months	[79]
Fujimi, 2021	case series	2	1F, 1M	68, 58	SDC	3+	IHC	M	trastuzumab + nab-paclitaxel, T-DM1, pertuzumab + docetaxel, trastuzumab + pertuzumab + eribulin/pertuzumab + docetaxel, T-DM1, trastuzumab + pertuzumab + eribulin	PR, PR, PR, CR/CR, CR, CR		[80]
Kawakita, 2022	retrospective	80	61M, 19F	57 (26–82)	SDC	2+,3+	IHC	R/M	trastuzumab + docetaxel	ORR 53 % pts, DOR 11.0 months	mOS 48 months, mPFS 9.2 months	[81]
Kinoshita, 2019	phase 2	16	3F, 13M	59 (26–72)	SDC	2+,3+	IHC, ISH	R/M	Trastuzumab + docetaxel	ORR 60.0 %	mPFS 8.5 m, mOS 33.8 m	[82]
Bando, 2021	phase I	17	NA	NA	SDC	2+, 3+	IHC/FISH or NGS	M	trastuzumab deruxtecan	ORR 47 % (8 PR, 9 SD), mDOR 12.9 months	PFS 14.1 months	[83]
Hanna, 2020	retrospective	9	6M, 3F	65 (45–87)	SDC	1+, 2+, 3+	IHC and FISH or NGS	adjuvant	Trastuzumab		mDFS 117 vs. 9 months; mOS 74 vs. 43 months	[22]

M = metastatic, R = recurrent, mOS = median overall survival, mPFS = median progression free survival, ORR = overall response rate, DOR = duration of response, SDC = salivary duct carcinoma, NA = not available, IHC = immunochemistry, FISH = fluorescence in situ hybridation, NGS = next generation sequencing, CR = complete response, PR = partial response, SD = stable disease, F = female, M = male, mTTP = median time to progression

of exatecan, a hexacyclic camptothecin analogue [86]. In breast cancer T-Dxd has showed a higher antitumor activity than T-DM1 reducing the risk of disease progression or death among patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane (DESTINY-Breast03) [87]. T-Dxd was approved by the FDA for patients with metastatic HER2 positive defined by an IHC score of 3 + or by an IHC score of 2 + and positive results on ISH breast cancer in 2019. In 2021, the U.S. FDA has also approved T-Dxd for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma.

Anti HER2 therapy benefits have not yet translated to patients with HER2 expression below this threshold. [88] Nevertheless, new ADC may be effective in HER2 low tumors (IHC 1 + or IHC 2 + and ISH negative) through its enzyme-cleavable antibody–drug linker, high drug-to-antibody ratio, and membrane-permeable payload. In the DESTINY-Breast04 trial, T-Dxd demonstrated improved outcomes over standard chemotherapy options in patients with HER2-low advanced breast cancer.

GQ1001 is another ADC composed of a mAb targeting human EGFR2 and conjugated, via a site-specific linker, to the cytotoxic maytansinoid mertansine (DM1).

A166 is an ADC composed of an anti-HER2 antibody and a highly potent MMAF-derived payload (duostatin-5) via a cleavable valine-citrulline linker [84]. A phase I trial showed that A166 had an acceptable toxicity profile and it was clinically effective in heavily pretreated patients with relapsed or refractory advanced solid cancers. The ORR of 36 % was achieved (NCT03602079) [89].

Ceralasertib is an oral inhibitor of the serine/threonine protein kinase Ataxia Telangiectasia and Rad3 Related (ATR), which is crucial to the cell's response to replication stress and genomic instability [90].

In the Table 2 ongoing clinical trials testing anti-HER2 therapies in adjuvant and metastatic setting are reported.

Future perspectives

The systemic treatment of SGCs has not changed over the last years. However, in some histologies, the knowledge of genomic profiling is needed for a tailored treatment, potentially improving the outcomes, both in adjuvant and recurrent/metastatic setting.

Indeed, given the previously discussed preliminary results based on phase 2 and retrospective studies (see Table 1), targeting HER2 could be beneficial for SGCs patients overexpressing HER2.

In breast cancer, new anti-HER2 agents, such as pertuzumab, or T-DM1 or T-Dxd demonstrated efficacy in HER2 positive patients. We strongly believe that these agents could play an important role in SGCs even if they need to be properly investigated, maybe avoiding some methodological issues such as the lack of any selection criterion and/or uniformly interpreting the positivity of HER2 expression (e.g. the

Table 2

Agent	Phase	Setting	Inclusion criteria	Status (5th March 2023)	Clinical trial number	Estimated Study Completion Date
T-DM1 (+CT/RT)	II	adjuvant	- resected stage II (with positive margins), III, IVA, or IVB locoregionally advanced salivary gland carcinoma (including any histologic subtype),HER2+ (2 + or 3 + by IHC; amplified by FISH, mutated on tumor genomic sequencing assay)	recruiting	NCT04620187	February 1, 2026
T-DM1 vs docetaxel + trastuzumab	II	metastatic (first line)	- recurrent/metastatic or unresectable SGCs (including any histologic subtype) - HER2 + (3 + by IHC, amplified by FISH or NGS)	recruiting	NCT05408845	July 31, 2028
trastuzumab deruxtecan	II (solid tumors)	metastatic	- unresectable and/or metastatic solid tumors eg: SGCs, colorectal, urothelial, gastric, hepatobiliary, endometrial, melanoma, ovarian, cervical, pancreatic, breast - HER2 mutations locally determined by NGS - prior HER2 targeted therapy is permitted.	active, not recruiting	NCT04639219	January 17, 2023
trastuzumab deruxtecan	II	metastatic	- recurrent and or metastatic salivary gland carcinoma -HER2 IHC 3 plus IHC 2 plus IHC 1 plus and or ISH plus	recruiting	jRCT2011210017	–
GQ1001	I (solid tumors)	metastatic	-advanced/unresectable or metastatic solid tumor with HER2-positive that is relapsed or refractory to standard therapy or for which there is no standard therapy and progressed.- HER2 + (2 + by IHC and amplified, 3 + by IHC, NGS or other analysis techniques)	recruiting	NCT04450732	May 1, 2024
A166	I/II (solid tumors)	metastatic	- locally advanced/metastatic solid tumors that did not respond or stopped responding to approved therapies -HER2 expressing is defined in this protocol as HER2 expression of ≥ 1 + determined by validated IHC, amplified by FISH or NGS	active, not recruiting	NCT03602079	December 2022
ceralasertib (AZD6738) + trastuzumab deruxtecan	I (solid tumors)	metastatic	- unresectable, advanced/metastatic disease - progressed on at least one line of systemic chemotherapy - progressed on at least 1 line of anti-HER2 therapy if eligible-HER2 expression (1–3 +) by IHC or amplified by FISH/NGS	recruiting	NCT04704661	March 31, 2026

expression of HER2 2 + found at IHC should be confirmed by ISH amplification).

ADC can be considered after progressive disease on trastuzumab and pertuzumab in the palliative setting, similarly to breast cancer practice. However, future research is needed to test these prosiming drugs in recurrent/metastatic SGC and in earlier disease.

In breast cancer, Licai He et al. demonstrated thar AR plays an important role in promoting the growth of HER2 positive through a cross-talk with the HER2 signaling. The authors concluded that anti-androgenic drugs may be used as an alternative second line therapy for treating HER2 + breast cancer [91]. L. He et al. revealed that Enzalutamide, an AR inhibitor, prevent the growth of HER2+ tumor disease in preclinical models. [91]This seems to suggest that the activity of anti-AR drugs might be anticipated in HER2 positive SGCs, even independently of anti HER2 drugs. [16]

Retrospective studies analyzing patients with AR-positive recurrent/metastatic SGCs have demonstrated an ORR of 18–67% with first-line ADT either single-agent LHRH analogs or AR antagonist (enzalutamide or bicalutamide), or LHRH analogue associated to bicalutamide [92–94]. However, the effective treatments in SGCs overexpressing both AR and HER2 is still unknown and further investigations are warranted.

Van Boxtel et al. [95] for the first time investigated the efficacy of adjuvant ADT in patients with poor-risk, staged as T4a/T4b (T4 or N2/N3 without distant metastases), AR-positive SDC, demonstrating a significantly longer DFS compared with the control group and a trend, although not significant, of better OS.

Beyond HER2 and AR expression, different molecular targets were studied. In other cancers, the correlation of molecular targets and therapy efficacy is well studied (e.g. the ER expression is associated with endocrine therapy benefit in breast cancers). The c-kit overexpression is identified as a molecular target but it is not clearly defined as a predictive biomarker of imatinib efficacy. In SGCs the role of these targets for therapeutic strategy is more controversial and there is limited clinical information about these patients.

The current evidence of anti-HER2 therapy as adjuvant setting derive from a retrospective study showing at a median follow-up of 5.6 years that 7 out of 9 patients treated with adjuvant chemotherapy associated to trastuzumab with concurrent RT, followed by up to 12 weeks of chemotherapy-trastuzumab and then trastuzumab alone completing 1 year of treatment, did not experience a disease relapse. The only two patients who progressed were both with low HER2 1+ [71]. The authors concluded that anti-HER2 therapy could be effective mostly among high risk patients with HER2 amplification and/or high positivity. Adjuvant anti-HER2 therapy could be a valid strategy for patients overexpressing HER2, but further prospective trials are necessary to define the optimal duration, the real efficacy, and the right treatment sequence. Indeed, international guidelines (Geiger 2021 ASCO) recommend use of anti HER2 targeted treatment in adjuvant setting only within clinical trial. The anti-HER2 therapeutic strategy could be potentially introduced in earlier setting combined with chemotherapy and being beneficial to reduce recurrence risk and to potentially prolong survival outcomes.

Conclusions

This review has provided a current overview of anti HER2 treatment including some insights of a perspective role of ADCs in HER2 positive SGCs, mainly represented by SDC and A-NOS.

SDC and ductal carcinoma of the breast share morphological and immunophenotypical similarities. While in breast cancer anti-HER2 therapy demonstrated a solid efficacy in HER2 positive obtained from large phase 3 randomized clinical trials, the benefit of HER2 therapy in SGCs is revealed from small retrospective studies and phase 2. This is recognized in rare cancers where research should be encouraged by clinical registries within networking and non-randomized clinical trials. [96]

Due to the complexity of methodological research in rare cancers the results obtained from other solid tumors sharing some morphological features should be translated into SGCs treatment strategy. This could apply both for selection of anti HER2 drugs and for the optimal sequence of such therapies.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Barnes L, Eveson J, Reichart P, Sidransky D. Pathology and genetics of head and neck tumours, vol. 9. IARC Press; 2007.
[2] Skálová A, Hyrcza MD, Leivo I. Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Salivary Glands. *Head Neck Pathol* 2022;16:40–53.
[3] Licitra L, Locati LD. Salivary gland cancer: from diagnosis to tailored treatment. Springer; 2019.
[4] Skálová A, 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;34:599–608.
[5] Nordkvist A, Gustafsson H, Juberg-Ode M, Stenman G. Recurrent rearrangements of 11q14–22 in mucoepidermoid carcinoma. Cancer Genet Cytogenet 1994;74:77–83.
[6] Fehr A, et al. A link between the expression of the stem cell marker HMGA2, grading, and the fusion CRTC1-MAML2 in mucoepidermoid carcinoma. Genes Chromosom Cancer 2009;48:777–85.
[7] Stephens PJ, et al. Whole exome sequencing of adenoid cystic carcinoma. J Clin Invest 2013;123:2965–8.
[8] Mitani Y, et al. Novel MYBL1 Gene Rearrangements with Recurrent MYBL1–NFIB Fusions in Salivary Adenoid Cystic Carcinomas Lacking t(6;9) Translocations. Clin Cancer Res 2016;22:725–33.
[9] Persson M, et al. Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck. Proc Natl Acad Sci USA 2009;106:18740–4.
[10] Van Herpen C, et al. Salivary gland cancer: ESMO-European Reference Network on Rare Adult Solid Cancers (EURACAN) Clinical Practice Guideline for diagnosis, treatment and follow-up. ESMO Open 2022;7:100602.
[11] Geiger JL, et al. Management of Salivary Gland Malignancy: ASCO Guideline. JCO 2021;39:1909–41.
[12] Dalin M, Watson P, Ho A, Morris L. Androgen Receptor Signaling in Salivary Gland Cancer. Cancers 2017;9:17.
[13] Mitani Y, et al. Alterations Associated with Androgen Receptor Gene Activation in Salivary Duct Carcinoma of Both Sexes: Potential Therapeutic Ramifications. Clin Cancer Res 2014;20:6570–81.
[14] Masubuchi T, et al. Clinicopathological significance of androgen receptor, HER2, Ki-67 and EGFR expressions in salivary duct carcinoma. Int J Clin Oncol 2015;20:35–44.
[15] Can NT, et al. Expression of Hormone Receptors and HER-2 in Benign and Malignant Salivary Gland Tumors. Head and Neck Pathol 2018;12:95–104.
[16] Cavalieri S, et al. HER2 status in recurrent/metastatic androgen receptor overexpressing salivary gland carcinoma patients. Front Oncol 2023;12:1096068.
[17] Egebjerg K, Harwood CD, Woller NC, Kristensen CA, Mau-Sørensen M. HER2 Positivity in Histological Subtypes of Salivary Gland Carcinoma: A Systematic Review and Meta-Analysis. Front Oncol 2021;11:693394.
[18] Nardi V, et al. Detection of Novel Actionable Genetic Changes in Salivary Duct Carcinoma Helps Direct Patient Treatment. Clin Cancer Res 2013;19:480–90.
[19] Locati LD, et al. Treatment relevant target immunophenotyping of 139 salivary gland carcinomas (SGCs). Oral Oncol 2009;45:986–90.
[20] Cornolti G, et al. Amplification and Overexpression of HER2/neu Gene and HER2/neu Protein in Salivary Duct Carcinoma of the Parotid Gland. Arch Otolaryngol Head Neck Surg 2007;133:1031.
[21] Glisson B, et al. HER2 Expression in Salivary Gland Carcinomas: dependence on hystological subtype. Clin Cancer Res 2004;10:944–6.
[22] Hanna GJ, et al. The Benefits of Adjuvant Trastuzumab for HER-2-Positive Salivary Gland Cancers. Oncologist 2020;25:598–608.
[23] Agulnik M, Siu L. An Update on the Systemic Therapy of Malignant Salivary Gland Cancers: Role of Chemotherapy and Molecular Targeted Agents. CMCACA 2004;4:543–51.
[24] Iqbal MS, Shaikh G, Chatterjee S, Cocks H, Kovarik J. Maintenance Therapy with Trastuzumab in Her2 Positive Metastatic Parotid Ductal Adenocarcinoma. Case Rep Oncol Med 2014;2014:1–4.
[25] Haddad R, et al. Herceptin in patients with advanced or metastatic salivary gland carcinomas. A phase II study. *Oral Oncology* 2003;39:724–7.

[26] Prat A, et al. Successful treatment of pulmonary metastatic salivary ductal carcinoma with trastuzumab-based therapy. Head Neck 2008;30:680–3.
[27] Skálová A, et al. Expression of HER-2/neu gene and protein in salivary duct carcinomas of parotid gland as revealed by fluorescence in-situ hybridization and immunohistochemistry. Histopathology 2003;42:348–56.
[28] Kaidar-Person O, Billan S, Kuten A. Targeted therapy with trastuzumab for advanced salivary ductal carcinoma: case report and literature review. Med Oncol 2012;29:704–6.
[29] Corrêa TS, Matos GDR, Segura M, dos Anjos CH. Second-Line Treatment of HER2-Positive Salivary Gland Tumor: Ado-Trastuzumab Emtansine (T-DM1) after Progression on Trastuzumab. Case Reports in Oncology 2018;11:252–7.
[30] Kramer-Marek G, Oyen WJG. Targeting the Human Epidermal Growth Factor Receptors with Immuno-PET: Imaging Biomarkers from Bench to Bedside. J Nucl Med 2016;57:996–1001.
[31] Takase S, et al. Biomarker immunoprofile in salivary duct carcinomas: clinicopathological and prognostic implications with evaluation of the revised classification. Oncotarget 2017;8:59023–35.
[32] Santana T, et al. Biomarker immunoprofile and molecular characteristics in salivary duct carcinoma: clinicopathological and prognostic implications. Hum Pathol 2019;93:37–47.
[33] Boon E, et al. A clinicopathological study and prognostic factor analysis of 177 salivary duct carcinoma patients from The Netherlands. Int J Cancer 2018;143:758–66.
[34] Press MF, et al. Amplification and overexpression of HER-2/neu in carcinomas of the salivary gland: correlation with poor prognosis. Cancer Res 1994;54:5675–82.
[35] Etges A, Pinto Jr DS, Kowalski LP, Soares FA, Araùjo VC. Salivary duct carcinoma: immunohistochemical profile of an aggressive salivary gland tumour. J Clin Pathol 2003;56:914–8.
[36] Nabili V, Tan JW, Bhuta S, Sercarz JA, Head CS. Salivary duct carcinoma: A clinical and histologic review with implications for trastuzumab therapy. Head Neck 2007;29:907–12.
[37] Sugano S, et al. Immunohistochemical Study of c-erbB-2 Oncoprotein Overexpression in Human Major Salivary Gland Carcinoma: An Indicator of Aggressiveness. The Laryngoscope 1992;102:923–7.
[38] Cho K-J, Lee S-S, Lee Y-S. Proliferating cell nuclear antigen and c-erbB-2 oncoprotein expression in adenoid cystic carcinomas of the salivary glands. Head Neck 1999;21:414–9.
[39] Jaehne M, et al. Clinical and immunohistologic typing of salivary duct carcinoma: A report of 50 cases. Cancer 2005;103:2526–33.
[40] Felix A, et al. Prognostic significance of biomarkers (c-erbB-2, p53, proliferating cell nuclear antigen, and DNA content) in salivary duct carcinoma. Hum Pathol 1996;27:561–6.
[41] Gilbert MR, et al. A 20-Year Review of 75 Cases of Salivary Duct Carcinoma. JAMA Otolaryngol Head Neck Surg 2016;142:489.
[42] Johnston ML, et al. Salivary duct carcinoma: Treatment, outcomes, and patterns of failure. Head Neck 2016;38:E820–6.
[43] Han MW, et al. Prognostic factors and outcome analysis of salivary duct carcinoma. Auris Nasus Larynx 2015;42:472–7.
[44] Arteaga CL, Engelman JA. ERBB receptors: from oncogene discovery to basic science to mechanism-based cancer therapeutics. Cancer Cell 2014;25:282–303.
[45] Wolff AC, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. JCO 2018;36:2105–22.
[46] Wolff AC, et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. JCO 2013;31:3997–4013.
[47] Cheng DT, et al. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A Hybridization Capture-Based Next-Generation Sequencing Clinical Assay for Solid Tumor Molecular Oncology. J Mol Diagn 2015;17:251–64.
[48] Ross DS, et al. Next-Generation Assessment of Human Epidermal Growth Factor Receptor 2 (ERBB2) Amplification Status: Clinical Validation in the Context of a Hybrid Capture-Based, Comprehensive Solid Tumor Genomic Profiling Assay. J Mol Diagn 2017;19:244–54.
[49] Ferguson DC, et al. ERBB2 amplification status in 67 salivary duct carcinomas assessed by immunohistochemistry, fluorescence in situ hybridization, and targeted exome sequencing. Mod Pathol 2022;35:895–902.
[50] Di Palma S, et al. Salivary duct carcinomas can be classified into luminal androgen receptor-positive, HER2 and basal-like phenotypes. Histopathology 2012;61:629–43.
[51] Williams MD, et al. Genetic and Expression Analysis of HER-2 and EGFR Genes in Salivary Duct Carcinoma: Empirical and Therapeutic Significance. Clin Cancer Res 2010;16:2266–74.
[52] Dogan S, et al. The repertoire of genetic alterations in salivary duct carcinoma including a novel HNRNPH3-ALK rearrangement. Hum Pathol 2019;88:66–77.
[53] Javaheripour A, Saatloo MV, Vahed N, Gavgani LF, Kouhsoltani M. Evaluation of HER2/neu expression in different types of salivary gland tumors: a systematic review and meta-analysis. JMedLife 2022;15:595–600.
[54] Limaye SA, et al. Trastuzumab for the Treatment of Salivary Duct Carcinoma. Oncologist 2013;18:294–300.
[55] Perissinotti AJ, et al. The role of trastuzumab in the management of salivary ductal carcinomas. Anticancer Res 2013;33:2587–91.
[56] De Block K, et al. Metastatic HER-2-positive salivary gland carcinoma treated with trastuzumab and a taxane: a series of six patients. Acta Clin Belg 2016;71:383–8.
[57] Takahashi H, et al. Phase II Trial of Trastuzumab and Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2–Positive Salivary Duct Carcinoma. JCO 2019;37:125–34.
[58] Agulnik M, et al. Phase II Study of Lapatinib in Recurrent or Metastatic Epidermal Growth Factor Receptor and/or erbB2 Expressing Adenoid Cystic Carcinoma and Non-Adenoid Cystic Carcinoma Malignant Tumors of the Salivary Glands. JCO 2007;25:3978–84.
[59] Kurzrock R, 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;31:412–21.
[60] Van Boxtel W, et al. Combination of docetaxel, trastuzumab and pertuzumab or treatment with trastuzumab-emtansine for metastatic salivary duct carcinoma. Oral Oncol 2017;72:198–200.
[61] Sorenson KR, Piovezani Ramos G, Villasboas Bisneto JC, Price K. Targeted Approaches Applied to Uncommon Diseases: A Case of Salivary Duct Carcinoma Metastatic to the Brain Treated with the Multikinase Inhibitor Neratinib. *Case Rep*. Oncol 2017;10:726–31.
[62] Kadowaki S, et al. Complete Response to Trastuzumab-Based Chemotherapy in a Patient with Human Epidermal Growth Factor Receptor-2-Positive Metastatic Salivary Duct Carcinoma ex Pleomorphic Adenoma. Case Rep Oncol 2013;6:450–5.
[63] Firwana B, Atassi B, Hasan R, Hasan N, Sukari A. Trastuzumab for Her2/neu-positive metastatic salivary gland carcinoma: Case report and review of the literature. Avicenna J Med 2012;2:71–3.
[64] Nashed M, Casasola RJ. Biological therapy of salivary duct carcinoma. J Laryngol Otol 2009;123:250–2.
[65] Sharon E, Kelly RJ, Szabo E. Sustained response of carcinoma ex pleomorphic adenoma treated with trastuzumab and capecitabine. Head Neck Oncol 2010;2:12.
[66] Locati LD, et al. Herceptin® plus chemotherapy in relapsed and/or metastatic salivary gland cancer. Oral Oncol 2005;41:97–8.
[67] Gibo T, Sekiguchi N, Gomi D, Noguchi T, Fukushima T, Kobayashi T, Ozawa T, Yamada SI, Koizumi T. Targeted therapy with trastuzumab for epidermal growth factor receptor 2 (HER2)-positive advanced salivary duct carcinoma: A case report. Mol Clin Oncol. 2019 Aug;11(2):111-115. doi: 10.3892/mco.2019.1875. Epub 2019 Jun 10. PMID: 31281644; PMCID: PMC6589940.
[68] Ghazali N, Parker L, Settle K, Lubek JE. Sustained response of HER2-positive metastatic salivary adenocarcinoma, not otherwise specified, treated with trastuzumab. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:292–9.
[69] Thorpe LM, et al. Significant and durable clinical benefit from trastuzumab in 2 patients with HER2-amplified salivary gland cancer and a review of the literature. Head Neck 2017;39.
[70] Lee JS, Kwon OJ, Park JJ, Seo JH. Salivary Duct Carcinoma of the Parotid Gland: Is Adjuvant HER-2–Targeted Therapy Required? J Oral Maxillofac Surg 2014;72:1023–31.
[71] Krishnamurthy J, et al. Salivary duct carcinoma responding to trastuzumab-based therapy: Case report and review of the literature. Head Neck 2013;35:E372–5.
[72] Falchook GS, Lippman SM, Bastida CC, Kurzrock R. Human epidermal receptor 2-amplified salivary duct carcinoma: Regression with dual human epidermal receptor 2 inhibition and anti-vascular endothelial growth factor combination treatment. Head Neck 2014;36:E25–7.
[73] Longo R, et al. HER2-positive metastatic, parotid salivary duct carcinoma treated with a trastuzumab/pertuzumab-based chemotherapy: A case report. Clin Case Rep 2020;8:2877–81.
[74] Jhaveri KL, et al. Ado-trastuzumab emtansine (T-DM1) in patients with HER2-amplified tumors excluding breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas: results from the NCI-MATCH trial (EAY131) subprotocol Q. Ann Oncol 2019;30:1821–30.
[75] Lee J, Park S, Jung HA, Lee SH, Seo S, Kim SB, Kim JW, Lee KW, Kang EJ, Kim JW, Choi YJ, Shim BY, An HJ, Park LC, Shin SH, Kim JJ, Oh SY, Kim MK, Ahn MJ. A phase 2 multicenter study of docetaxel-PM and trastuzumab-pkrb combination therapy in recurrent or metastatic salivary gland carcinomas. Cancer. 2023 Oct 1;129(19):2966-2974. doi: 10.1002/cncr.34892. Epub 2023 May 28. PMID: 37246414.
[76] Sousa LG, et al. Treatment patterns and outcomes of palliative systemic therapy in patients with salivary duct carcinoma and adenocarcinoma, not otherwise specified. Cancer 2022;128:509–18.
[77] Taha T, Billan S. Case report: ado-trastuzumab as second-line treatment in HER2 positive salivary duct carcinoma. Anticancer Drugs 2022;33:e760–3.
[78] Ma P, et al. Anti-PD-1 plus anti-HER2 and chemotherapy showed superior and durable clinical benefit in a patient with advanced salivary duct carcinoma. Oral Oncol 2022;130:105905.
[79] Uijen MJM, Lassche G, Van Engen-van Grunsven ACH, Driessen CML, Van Herpen CML. Case series of docetaxel, trastuzumab, and pertuzumab (DTP) as first line anti-HER2 therapy and ado-trastuzumab emtansine (T-DM1) as second line for recurrent or metastatic HER2-positive salivary duct carcinoma. Oral Oncol 2022;125:105703.
[80] Fujimi A, et al. Eribulin in combination with HER2-targeted antibodies for successful treatment of metastatic salivary duct carcinoma: A report of two cases. Oral Oncol 2021;120:105287.
[81] Kawakita D, et al. Survival benefit of HER2-targeted or androgen deprivation therapy in salivary duct carcinoma. Ther Adv Med Oncol 2022;14.175883592211195.
[82] Kinoshita I, et al. Abstract CT137: Phase II study of trastuzumab and docetaxel therapy in patients with HER2-positive recurrent and/or metastatic salivary gland carcinoma. Cancer Res 2019;79:CT137.

[83] Bando H, 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. JCO 2021;39:6079.
[84] Yu J, Fang T, Yun C, Liu X, Cai X. Antibody-Drug Conjugates Targeting the Human Epidermal Growth Factor Receptor Family in Cancers. Front Mol Biosci 2022;9:847835.
[85] Thomas A, Teicher BA, Hassan R. Antibody–drug conjugates for cancer therapy. Lancet Oncol 2016;17:e254–62.
[86] Xu Z, et al. Novel HER2-Targeting Antibody-Drug Conjugates of Trastuzumab Beyond T-DM1 in Breast Cancer: Trastuzumab Deruxtecan(DS-8201a) and (Vic-) Trastuzumab Duocarmazine (SYD985). Eur J Med Chem 2019;183:111682.
[87] Cortés J, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med 2022;386:1143–54.
[88] Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, Tsurutani J, Ueno NT, Prat A, Chae YS, Lee KS, Niikura N, Park YH, Xu B, Wang X, Gil-Gil M, Li W, Pierga JY, Im SA, Moore HCF, Rugo HS, Yerushalmi R, Zagouri F, Gombos A, Kim SB, Liu Q, Luo T, Saura C, Schmid P, Sun T, Gambhire D, Yung L, Wang Y, Singh J, Vitazka P, Meinhardt G, Harbeck N, Cameron DA; DESTINY-Breast04 Trial Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20. doi: 10.1056/NEJMoa2203690. Epub 2022 Jun 5. PMID: 35665782; PMCID: PMC10561652.
[89] Liu Y, et al. A first in-human study of A166 in patients with locally advanced/metastatic solid tumors which are HER2-positive or HER2-amplified who did not respond or stopped responding to approved therapies. JCO 2020;38:1049.
[90] Yap TA, et al. Ceralasertib (AZD6738), an Oral ATR Kinase Inhibitor, in Combination with Carboplatin in Patients with Advanced Solid Tumors: A Phase I Study. Clin Cancer Res 2021;27:5213–24.
[91] He L, et al. Targeting Androgen Receptor in Treating HER2 Positive Breast Cancer. Sci Rep 2017;7:14584.
[92] Boon E, 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;40:605–13.
[93] Viscuse PV, Price KA, Garcia JJ, Schembri-Wismayer DJ, Chintakuntlawar AV. 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.
[94] Locati LD, et al. Clinical activity of androgen deprivation therapy in patients with metastatic/relapsed androgen receptor-positive salivary gland cancers. Head Neck 2016;38:724–31.
[95] Van Boxtel W, et al. Adjuvant androgen deprivation therapy for poor-risk, androgen receptor–positive salivary duct carcinoma. Eur J Cancer 2019;110:62–70.
[96] Europe RC. Rare Cancer Agenda 2030. (Youcanprint; 2020.