Molecular Therapeutic Targets for Adenoid Cystic Carcinoma

Subjects: Otorhinolaryngology

Contributor: Lauren Miller , , Vivienne Au , Daniel Faden

Adenoid Cystic Carcinoma (ACC) is a rare malignant tumor of the salivary glands. The most researched pathway associated with ACC is the MYB–NFIB translocation, found to lead to dysregulation of critical cellular pathways and thought to be a fundamental driver in a subset of ACC disease pathogenesis. Other notable molecular targets that have been studied include the cKIT receptor, the epidermal growth factor receptor (EGFR) pathway, and NOTCH1, all with limited efficacy in clinical trials. The ongoing investigation of molecular abnormalities underpinning ACC that may be responsible for carcinogenesis is critical to identifying and developing novel targeted therapies.

Immune Adenoid cystic carcinoma Therapeutic Targets

1. Mutation Burden and Profile

Adenoid Cystic Carcinomas (ACCs) have been shown to possess a low mutational burden across numerous studies, matching their indolent clinical behaviors. Using a cohort of 60 tumor samples and performing exome and whole-genome sequencing, Ho et al. found ACCs to have low mutational burden compared to other common head and neck cancers, such as head and neck squamous cell carcinoma (mean 22 coding mutations vs. 130, respectively) [1][2]. It is identified common alterations in chromatin regulation genes [1], as well as orthogonal pathways such as histone acetyltransferase/deacetylase function, and DNA damage response [2]. Similarly, Rettig et al. studied 25 ACC samples using whole-genome sequencing (WGS) and found a median of 14 mutations per tumor (range 2–36) and again, recurrent alterations in chromatin remodeling genes such as SMARCA2, MLL2, and KDM6A [3]. Potential mutational differences in 1045 ACC tissue samples in patients with primary (*n* = 177) versus recurrent or metastatic (R/M) (*n* = 868) ACC were evaluated using WGS and next-generation sequencing. Notable differences between the two patient groups included significantly increased mutational burden across the NOTCH gene family, chromatin-remodeling genes, tumor suppressor genes, and DNA damage repair genes in R/M cases [4].

2. MYB

MYB is a transcription factor studied for its known roles in oncogenesis, broadly including cell proliferation and survival [5]. Prior literature has focused on the MYB pathway's involvement in the ACC mutational landscape, and there is significant evidence for its role in ACC tumorigenesis [6]. Specifically, MYB has been found as a fusion oncogene with nuclear factor 1 transcription family (NFIB) in ACC with a t(6;9)(q23.3;p22.3) translocation [2][4]. In

studies characterizing structural variants of ACC using whole-genome sequencing, MYB translocations were the only recurrent structural variants identified, reaffirming its significance [1]. Drier et al. investigated ACC translocations in detail using whole-genome sequencing and demonstrated that repositioning of regulatory elements adjacent to MYB triggered overexpression. This group identified several distinct chromosomal rearrangements, placing super-enhancers adjacent to the MYB locus, and demonstrated that these enhancers directly interact with MYB. Interestingly, when studying how MYB may impact ACC histological classifications (i.e., tubular vs. cribriform vs. solid), unique regulatory and signaling pathways involving TP63 and NOTCH were identified [7].

Another study by Hanna et al. evaluating R/M ACC identified MYB overexpression or rearrangement in 24 of 55 samples [8]. The 10-year overall survival in the MYB-altered subgroup was 100%, the highest of any identified alteration in their cohort [8]. Rettig et al. identified the MYB–NFIB fusion oncogene in 11 of 25 tissue samples. NFIB translocations occurred in 15 of 25 samples, sometimes involving genes besides MYB, suggesting the possible role of NFIB in oncogenesis independent of MYB [3]. However, these samples with NFIB fusions independent of MYB were not confirmed on mRNA expression analysis [3]. In a separate WGS study of eight ACC samples, Thyparambil et al. reported a single sample with fusions of MYBL–NFIB or AHI1–NFIB, in agreement with the aforementioned hypothesis [9][10].

The MYBL1–NFIB fusion is seen less frequently than MYB–NFIB but is similarly known to encourage oncogenic overactivity [11] and thought to have similar oncogenic properties as the MYB–NFIB fusion [12]. In a separate sample with Saida et al., 45 of 52 ACC samples were found to contain translocations in MYB, MYBL1, and NFIB detected via fluorescence in situ hybridization (FISH) [13]. Translocations in ACC tumors fusing the MYBL1 gene to the NFIB and RAD51B genes demonstrated similar outcomes to MYB translocations, suggesting a potential interchangeable nature to these drivers of ACC [14].

Despite the high rate of translocation and mutation of MYB in ACC, actionable targets acting along this pathway have had little success. There has been some discovery in vitro research to understand potential targets to the MYB pathway. Recent work by Yusenko et al. evaluated a MYB inhibitory compound, Bcr–TMP, that acts as a highly active MYB inhibitory compound, demonstrating anti-proliferative effects on ACC cells [15]. This same group further identified inhibition of MYB through proteasome inhibitors; further analysis of one such proteasome inhibitor, oprozomib, interfered with MYB stimulatory activity [16]. Hanna et al. investigated the use of Tretinoin (all-trans retinoic acid) in patients with R/M ACC, as the retinoic acid receptor has been suggested to play a role in the downregulation of MYB expression in studies on myeloid leukemia. No response in 18 patients and a median progression-free survival of 3.2 months [17]. Andersson et al. identified that IGF1R/AKT inhibition downregulated MYB–NFIB activity in ACC models, suggesting a potential strategy to target transcriptional regulation in ACC [18]. His group more recently identified the DNA-damage sensor kinase ATR as a downstream therapeutic target of MYB that appears to be overexpressed in primary ACCs. Further, treatment with an ATR kinase inhibitor (VX-970) demonstrated a dose-dependent decrease in proliferation and induced apoptosis in MYB-positive ACC cells.

3. cKIT

cKIT is a receptor tyrosine kinase involved in intracellular signaling and cellular deregulation with known roles in the development of leukemia, melanoma, thyroid cancer, and breast cancer [19]. The role of cKIT in ACC has been extensively studied. Many patients with ACC have demonstrated overexpression of cKIT, thought to range from 60 to 90% of ACC tumors [20][21]. A study by Vila et al. in 2009 was the first to examine the cKIT gene mutation in primary ACC, with cKIT missense point mutations detected in seven of eight samples (88%) [22]. The identification of gain-of-function mutations in exon 11, and less frequently in exons 9, 13 and 17, suggested tyrosine kinase inhibitors as a potential treatment for ACC. Copy number variations in cKIT have also been investigated. Freier et al. performed fluorescent in situ hybridization (FISH) on ACC samples found to express cKIT. In this cohort, 6% of ACC tumors demonstrated a cKIT copy number gain, suggesting that a gain in gene copy number may explain increased cKIT protein expression in a limited subset of ACC pathogenesis [23].

Targeted therapies against the cKIT receptor using tyrosine kinase inhibitors were one of the first attempts of precision therapy in patients with ACC, specifically using imatinib, dasatinib, or sunitinib therapy. Unfortunately, while high cKIT expression in ACC has been well established, these studies were largely disappointing, with an overall response rate (ORR) below 5% and no significant improvement in patient survival in any of these trials [24][25][26][27].

In a phase II trial for imatinib, ten patients with advanced or metastatic ACC cKIT-positive tumors were enrolled in daily dosing of imatinib at 400 mg/day, without any responses, and eight of the ten with disease progression after a median of 6 months [24]. In a separate phase II trial, no objective responses were appreciated in 15 patients with the same dosing of imatinib [25]. A separate study explored the efficacy of imatinib with cisplatin for patients with ACC with a known overexpression of cKIT. Response to treatment was followed with imaging, demonstrating a partial response in 3 of 28 patients and 19 of 28 patients with stable disease [28]. Notably, their cohort overall survival was 35 months.

Wong et al. studied the efficacy of dasatinib in 40 patients with ACC and cKIT-positive tumors determined by immunohistochemistry [26]. Only one objective response (2.5%) was reported. Twenty patients (50%) had stable disease and 29 eventually experienced disease progression. Mean progression-free survival was 4.8 months. Median survival for this cohort was 14.5 months, with a six-month survival rate of 81.5%.

In the response of R/M ACC patients to daily sunitinib, there were no objective responses in 13 patients, with median OS of 18.7 months [27]. These largely disappointing findings have led many investigators to conclude that the cKIT pathway is not a primary driver in ACC tumorigenesis.

4. Epidermal growth factor receptor (EGFR)

Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor which, when activated, stimulates mitosis and leads to cell proliferation. EGFR is overexpressed in a variety of tumors and it is thought to be overexpressed in up to 85% of ACC, making it a therapeutic target of interest [29]. The immunohistochemical

expression of EGFR in ACC tumors has been characterized; in a study of 25 ACC samples, EGFR expression was quantified as weak-moderate in 32% and as strong in 64% of samples [30].

Prior studies have targeted the EGFR pathway via numerous therapeutic agents including gefitinib [31], cetuximab [29], and lapatinib [32] without meaningful response rates in previously treated patients. Specifically, for cetuximab, no patients with ACC (n = 23) demonstrated a meaningful response, with 12 of 23 patients having disease stabilization greater than 6 months [29]. In another study of 19 patients with advanced ACC, lapatinib [32], a small molecule with dual EGFR and erbB2 tyrosine kinase activity, was studied. No responses were observed in this patient population; 15 patients demonstrated disease stabilization of 6 months or greater.

5. Fibroblast Growth Factor Receptor 1 (FGFR1)

Fibroblast growth factor receptor 1 (FGFR1) is a downstream pathway from the MYB gene and upregulation can lead to overexpression of FGF in patients with ACC [33]. Dovitinib, a small molecular inhibitor of FGFR1, was assessed for possible therapeutic effect in patients with advanced ACC and had a partial response rate and disease stabilization rate of 6% and 65%, respectively [34][35].

Lenvatinib is a new-generation multi-kinase inhibitor against FGFR1-3, VEGFR2, cKIT, RET and PDGFR alpha and beta, and has been found to have more promising results [35]. To date, two separate studies by Locati et al. and Tchekmedyian et al. have investigated the efficacy of lenvatinib in R/M ACC. Locati et al. evaluated 26 patients in their cohort, noting a partial response rate of 12% (n = 3). In patients with stable disease (n = 20), tumor shrinkage by radiographic evaluation was reported to be approximately 25% in 4 patients. Dose adjustment was required in the vast majority of patients (92%). The median progression-free survival and OS were 9.1 months and 27 months, respectively [36]. Similarly, Tchekmedyian et al. reported a partial response rate of 15.6% in 32 patients with R/M ACC. Eight (25%) patients had more than 20% reduction in tumor size [37]. At least one dosage modification was required in 72% of patients. The median progression-free survival was reported to be 17.5 months.

In light of these results, lenvatinib was designated a National Comprehensive Cancer Network (NCCN) grade 2b [38] recommendation (NCCN panel vote of at least 50–85%), for treatment of progressive or R/M ACC in the NCCN Head and Neck Cancers guidelines V.1.2020 [39]. In an ongoing phase II study, the efficacy of combination lenvatinib and pembrolizumab therapy in treating advanced ACC and other salivary gland cancers is currently underway[40].

6. Vascular Endothelial Growth Factor (VEGF)

Vascular endothelial growth factor (VEGF) has been assessed for a potential role in ACC disease progression, given the role of other growth factors as described above as well as its role in tumor angiogenesis. In prior studies assessing ACC tumor samples, VEGF expression was considered a poor prognostic factor for tumor stage [41] as well as overall survival [42][43].

Pazopanib, a small molecule inhibitor of VEGFR, PDGFR, and KIT, has previously been assessed for antitumor activity in ACC patients with underwhelming results, including 1 of 46 patients demonstrating a partial response and 35 of 46 with stable disease [44]. The median progression-free survival and overall survival were reported at 5.9 months and 16.6 months, respectively.

7. NOTCH1

The NOTCH signaling pathway is a well-known critical regulator of cell proliferation and survival. In particular, mutation of the NOTCH1 gene has been shown to play a role in R/M ACC, possibly via induction of neoangiogenesis as the mechanism of tumor growth [45]. Further, NOTCH1 has been found to be heavily mutated across ACC [4]. Patients who exhibited NOTCH1 mutations in ACC samples have been associated with an overall shorter survival [46]. Activating NOTCH1 is present in approximately 20% of ACC and is associated with a more aggressive disease course with higher rates of bone and liver metastases [47]. Chintakuntlawar et al. reviewed genetic testing results for 23 ACC patients and identified 41 unique mutations, among which 22% (5/23) demonstrated NOTCH mutations [48].

Additional literature has suggested increased rates of NOTCH mutation in R/M cases. For example, Ho et al. demonstrated a significantly higher proportion of NOTCH1 mutations in R/M cases of ACC compared to primary cases [4]. Similarly, Su et al. noted higher expression levels of NOTCH1 in R/M ACC cases as compared to primary ACC tumors [49]. Activated NOTCH1 upregulates genes such as BCL-2 and CCND1, well-known anti-apoptotic and cell cycle-related genes, which suggests a possible role of NOTCH1 in metastatic ACC.

Mouse models with NOTCH1 mutants receiving specific monoclonal antibodies targeting NOTCH1 have demonstrated partial responses in ACC tumor size [47]. However, human phase I trials have demonstrated minimal responses, with ranging therapeutic toxicities [50]. A phase I trial studying bronticuzumab, the monoclonal antibody against Notch1, demonstrated 6 of 36 ACC subjects had either a partial or prolonged period of disease stabilization (NCT01778439) [51][52]. A phase I trial of the small-molecule CB-103, an upstream inhibitor of the NOTCH pathway, is also being studied with preliminary data demonstrating a median progression-free survival of 22 weeks in ACC patients (NCT03422679) [53]. The preliminary results from the ACCURACY trial, an open-label, multicenter study of AL101, a small molecule selective gamma-secretase inhibitor that blocks Notch signaling, demonstrated early disease activity with a response rate of 15% [54].

8. Estrogen Receptor

Several studies have investigated the possibility of estrogen receptor blockade as a therapeutic target for ACC. Estrogen receptor (ER)-beta subtype has been found to be expressed in salivary gland cells, and it is hypothesized that estrogen may regulate salivary gland physiology [55]. Another report found significantly increased ER-beta nuclear expression in 32 of 38 cases of ACC [56]. However, to date, it is unclear what role increased ER-beta

subtypes plays with regard to ACC tumorigenesis, or the feasibility of estrogen receptor blockage as a therapeutic target for ACC.

9. PI3K/PTEN/mTOR Pathway

The PI3K/PTEN/mTOR pathway is a complex pathway that transmits proliferative intracellular signals from membrane-bound receptors [57]. Various components of this pathway have been explored for their roles in ACC pathogenesis. In a phase II study of everolimus, an mTOR receptor inhibitor, to treat progressive unresectable ACC, everolimus showed promising efficacy. Among 34 enrolled patients, median progression-free survival was 11.2 months with 27 patients showing stable disease and tumor shrinkage seen in 15 subjects [58]. Results from a recent phase I study investigating the combined effects of lenalidomide in combination with everolimus demonstrated this combination to be safe and tolerable with particular excitement for their efficacy in ACC [59].

The FGF/IGF/PI3K pathway has been a target for prior study in ACC, with Ho et al. identifying recurrent mutations in 30% of ACC tumors in this pathway [1].

PTEN has been studied extensively as one of the most important tumor suppressors in human cancers; inhibition of PTEN promotes tumorigenesis. Liu et al. reported that loss of PTEN expression was most frequently seen in ACC as compared to other salivary gland malignancies, representing 26 of 55 of ACC samples, especially in the poorly differentiated, high-grade subtype of solid ACC (18/22) [60].

Yu et al. found the expression of p-S6 (downstream molecule of mTOR), p-Stat3, PAI, EGFR and HIF-1a was significantly increased in 72 ACC samples, compared with 12 pleomorphic adenoma and 18 normal salivary glands tissues, suggesting possible mTOR downstream inhibitors as ACC therapy targets [61].

References

1. Ho, A.S.; Kannan, K.; Roy, D.M.; Morris, L.G.T.; Ganly, I.; Katabi, N.; Ramaswami, D.; Walsh, L.; Eng, S.; Huse, J.T.; et al. The mutational landscape of adenoid cystic carcinoma. Nat. Genet. 2013, 45, 791–798.
2. Stransky, N.; Egloff, A.M.; Tward, A.D.; Kostic, A.D.; Cibulskis, K.; Sivachenko, A.; Kryukov, G.V.; Lawrence, M.S.; Sougnez, C.; McKenna, A.; et al. The Mutational Landscape of Head and Neck Squamous Cell Carcinoma. Science 2011, 333, 1157–1160.
3. Rettig, E.M.; Talbot, C.C.; Sausen, M.; Jones, S.; Bishop, J.A.; Wood, L.D.; Tokheim, C.; Niknafs, N.; Karchin, R.; Fertig, E.; et al. Whole-Genome Sequencing of Salivary Gland Adenoid Cystic Carcinoma. Cancer Prev. Res. 2016, 9, 265–274.

4. Ho, A.S.; Ochoa, A.; Jayakumaran, G.; Zehir, A.; Mayor, C.V.; Tepe, J.; Makarov, V.; Dalin, M.G.; He, J.; Bailey, M.; et al. Genetic hallmarks of recurrent/metastatic adenoid cystic carcinoma. J. Clin. Investig. 2019, 129, 4276–4289.
5. Ramsay, R.G.; Gonda, T.J. MYB function in normal and cancer cells. Nat. Rev. Cancer 2008, 8, 523–534.
6. Ferrarotto, R.; Heymach, J.V.; Glisson, B.S. MYB-fusions and other potential actionable targets in adenoid cystic carcinoma. Curr. Opin Oncol. 2016, 28, 195–200.
7. Drier, Y.; Cotton, M.J.; Williamson, K.E.; Gillespie, S.; Ryan, R.; Kluk, M.J.; Carey, C.D.; Rodig, S.J.; Sholl, L.M.; Afrogheh, A.H.; et al. An oncogenic MYB feedback loop drives alternate cell fates in adenoid cystic carcinoma. Nat. Genet. 2016, 48, 265–272.
8. Hanna, G.J.; Bae, J.E.; Lorch, J.H.; Schoenfeld, J.D.; Margalit, D.N.; Tishler, R.B.; Haddad, R.I.; Chau, N.G. Long-term outcomes and clinicogenomic correlates in recurrent, metastatic adenoid cystic carcinoma. Oral Oncol. 2020, 106, 104690.
9. Thyparambil, S.P.; Kim, Y.J.; Chambers, A.; Yan, D.; Sellappan, S.; Gong, C.; Sedgewick, A.; Newton, Y.; Sanborn, J.Z.; Vaske, C.J.; et al. Comprehensive proteomic and genomic profiling to identify therapeutic targets in adenoid cystic carcinoma. J. Clin. Oncol. 2018, 36, 6053.
10. Thyparambil, S.P.; Kim, Y.J.; Chambers, A.G.; Yan, N.; Sellappan, S.; Sedgewick, A.J.; Newton, Y.; Sanborn, J.Z.; Vaske, C.J.; Benz, S.C.; et al. Abstract 778: Potential drug targets for adenoid cystic carcinoma elucidated by proteogenomic analysis. In Experimental and Molecular Therapeutics; American Association for Cancer Research: Philadelphia, PA, USA, 2018; Volume 78, p. 778.
11. Goleva, E.; Lyubchenko, T.; Kraehenbuehl, L.; Lacouture, M.E.; Leung, D.Y.; Kern, J.A. Our current understanding of checkpoint inhibitor therapy in cancer immunotherapy. Ann. Allergy Asthma Immunol. 2021, 126, 630–638.
12. Andersson, M.K.; Mangiapane, G.; Nevado, P.T.; Tsakaneli, A.; Carlsson, T.; Corda, G.; Nieddu, V.; Abrahamian, C.; Chayka, O.; Rai, L.; et al. ATR is a MYB regulated gene and potential therapeutic target in adenoid cystic carcinoma. Oncogenesis 2020, 9, 5–10.
13. Saida, K.; Murase, T.; Ito, M.; Fujii, K.; Takino, H.; Masaki, A.; Kawakita, D.; Ijichi, K.; Tada, Y.; Kusafuka, K.; et al. Mutation analysis of the EGFR pathway genes, EGFR, RAS, PIK3CA, BRAF, and AKT1, in salivary gland adenoid cystic carcinoma. Oncotarget 2018, 9, 17043–17055.
14. Brayer, K.J.; Frerich, C.A.; Kang, H.; Ness, S.A. Recurrent fusions in MYB and MYBL1 define a common, transcription factor-driven oncogenic pathway in salivary gland adenoid cystic carcinoma. Cancer Discov. 2016, 6, 176–187.
15. Yusenko, M.V.; Biyanee, A.; Frank, D.; Köhler, L.H.F.; Andersson, M.K.; Khandanpour, C.; Schobert, R.; Stenman, G.; Biersack, B.; Klempnauer, K.-H. Bcr-TMP, a Novel Nanomolar-Active

Compound That Exhibits Both MYB- and Microtubule-Inhibitory Activity. Cancers 2021, 14, 43.

16. Yusenko, M.V.; Biyanee, A.; Andersson, M.K.; Radetzki, S.; von Kries, J.P.; Stenman, G.; Klempnauer, K.-H. Proteasome inhibitors suppress MYB oncogenic activity in a p300-dependent manner. Cancer Lett. 2021, 520, 132–142.
17. Hanna, G.J.; Oneill, A.; Cutler, J.M.; Flynn, M.; Vijaykumar, T.; Clark, J.R.; Wirth, L.J.; Lorch, J.H.; Park, J.C.; Mito, J.K.; et al. A phase II trial of all-trans retinoic acid (ATRA) in advanced adenoid cystic carcinoma. Oral Oncol. 2021, 119, 105366.
18. Andersson, M.K.; Afshari, M.K.; Andrén, Y.; Wick, M.J.; Stenman, G. Targeting the Oncogenic Transcriptional Regulator MYB in Adenoid Cystic Carcinoma by Inhibition of IGF1R/AKT Signaling. J. Natl. Cancer Inst. 2017, 109, djx017.
19. Babaei, M.A.; Kamalidehghan, B.; Saleem, M.; Huri, H.Z.; Ahmadipour, F. Receptor tyrosine kinase (c-Kit) inhibitors: A potential therapeutic target in cancer cells. Drug Des. Devel. Ther. 2016, 10, 2443–2459.
20. Holst, V.A.; Marshall, C.E.; Moskaluk, C.A.; Frierson, H.F. Kit protein expression and analysis of c-kit gene mutation in adenoid cystic carcinoma. Mod. Pathol. 1999, 12, 956–960.
21. Cros, J.; Sbidian, E.; Hans, S.; Roussel, H.; Scotte, F.; Tartour, E.; Brasnu, D.; Laurent-Puig, P.; Bruneval, P.; Blons, H.; et al. Expression and mutational status of treatment-relevant targets and key oncogenes in 123 malignant salivary gland tumours. Ann. Oncol. 2013, 24, 2624–2629.
22. Vila, L.; Liu, H.; Al-Quran, S.Z.; Coco, D.P.; Dong, H.J.; Liu, C. Identification of c-kit gene mutations in primary adenoid cystic carcinoma of the salivary gland. Mod. Pathol. 2009, 22, 1296–1302.
23. Freier, K.; Flechtenmacher, C.; Walch, A.; Devens, F.; Mühling, J.; Lichter, P.; Joos, S.; Hofele, C. Differential KIT expression in histological subtypes of adenoid cystic carcinoma (ACC) of the salivary gland. Oral Oncol. 2005, 41, 934–939.
24. Pfeffer, M.R.; Talmi, Y.; Catane, R.; Symon, Z.; Yosepovitch, A.; Levitt, M. A phase II study of Imatinib for advanced adenoid cystic carcinoma of head and neck salivary glands. Oral Oncol. 2007, 43, 33–36.
25. Hotte, S.J.; Winquist, E.W.; Lamont, E.; MacKenzie, M.; Vokes, E.; Chen, E.X.; Brown, S.; Pond, G.R.; Murgo, A.; Siu, L.L. Imatinib Mesylate in Patients with Adenoid Cystic Cancers of the Salivary Glands Expressing c-kit: A Princess Margaret Hospital Phase II Consortium Study. J. Clin. Oncol. 2005, 23, 585–590.
26. Wong, S. Phase II trial of dasatinib for recurrent or metastatic c-KIT expressing adenoid cystic carcinoma and for nonadenoid cystic malignant salivary tumors. Ann. Oncol. 2016, 27, 318–323.

27. Chau, N.G.; Hotte, S.J.; Chen, E.X.; Chin, S.F.; Turner, S.; Wang, L.; Siu, L.L. 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, 1562–1570.
28. Ghosal, N.; Mais, K.; Shenjere, P.; Julyan, P.; Hastings, D.; Ward, T.; Ryder, W.D.; Bruce, I.; Homer, J.; Slevin, N.J. Phase II study of cisplatin and imatinib in advanced salivary adenoid cystic carcinoma. Br. J. Oral Maxillofac. Surg. 2011, 49, 510–515.
29. Locati, L.D.; Bossi, P.; Perrone, F.; Potepan, P.; Crippa, F.; Mariani, L.; Casieri, P.; Orsenigo, M.; Losa, M.; Bergamini, C.; et al. Cetuximab in recurrent and/or metastatic salivary gland carcinomas: A phase II study. Oral Oncol. 2009, 45, 574–578.
30. Dahse, R.; Driemel, O.; Schwarz, S.; Kromeyer-Hauschild, K.; Berndt, A.; Kosmehl, H. KRAS status and epidermal growth factor receptor expression as determinants for anti-EGFR therapies in salivary gland carcinomas. Oral Oncol. 2009, 45, 826–829.
31. Jakob, J.A.; Kies, M.S.; Glisson, B.S.; Kupferman, M.E.; Liu, D.D.; Lee, J.J.; El-Naggar, A.K.; Gonzalez-Angulo, A.M.; Blumenschein, G.R., Jr. Phase II study of gefitinib in patients with advanced salivary gland cancers. Head Neck 2014, 37, 644–649.
32. Agulnik, M.; Cohen, E.W.; Cohen, R.B.; Chen, E.X.; Vokes, E.E.; Hotte, S.J.; Winquist, E.; Laurie, S.; Hayes, D.N.; Dancey, J.E.; et al. Phase II Study of Lapatinib in Recurrent or Metastatic Epidermal Growth Factor Receptor and/or erbB2 Expressing Adenoid Cystic Carcinoma and Non–Adenoid Cystic Carcinoma Malignant Tumors of the Salivary Glands. J. Clin. Oncol. 2007, 25, 3978–3984.
33. Hotte, S.; Hao, D.; Pond, G.; Laurie, S.; Winquist, E.; Filion, M.; Levine, M. Dovitinib in advanced adenoid cystic carcinoma of the salivary glands: Ontario Clinical Oncology Group DOVE trial. Ann. Oncol. 2016, 27, vi335.
34. Dillon, P.M.; Petroni, G.R.; Horton, B.J.; Moskaluk, C.A.; Fracasso, P.M.; Douvas, M.G.; Varhegyi, N.; Zaja-Milatovic, S.; Thomas, C.Y. A Phase II Study of Dovitinib in Patients with Recurrent or Metastatic Adenoid Cystic Carcinoma. Clin. Cancer Res. 2017, 23, 4138–4145.
35. Schvartsman, G.; Pinto, N.A.; Bell, D.; Ferrarotto, R. Salivary gland tumors: Molecular characterization and therapeutic advances for metastatic disease. Head Neck 2019, 41, 239–247.
36. Locati, L.D.; Galbiati, D.; Calareso, G.; Alfieri, S.; Singer, S.; Cavalieri, S.; Bergamini, C.; Bossi, P.; Orlandi, E.; Resteghini, C.; et al. Patients with adenoid cystic carcinomas of the salivary glands treated with lenvatinib: Activity and quality of life. Cancer 2020, 126, 1888–1894.
37. Tchekmedyian, V.; Sherman, E.J.; Dunn, L.; Tran, C.; Baxi, S.; Katabi, N.; Antonescu, C.R.; Ostrovnaya, I.; Haque, S.S.; Pfister, D.G.; et al. Phase II study of lenvatinib in patients with

progressive, recurrent or metastatic adenoid cystic carcinoma. J. Clin. Oncol. 2019, 37, 1529–1537.

38. Tchekmedyian, V. Salivary Gland Cancers. Hematol. Oncol. Clin. N. Am. 2021, 35, 973–990.
39. Pfister, D.G.; Spencer, S.; Adelstein, D.; Adkins, D.; Anzai, Y.; Brizel, D.M.; Bruce, J.Y.; Busse, P.M.; Caudell, J.J.; Cmelak, A.J.; et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J. Natl. Compr. Cancer Netw. 2020, 18, 873–898.
40. Memorial Sloan Kettering Cancer Center. Lenvatinib and Pembrolizumab in People with Advanced Adenoid Cystic Carcinoma and Other Salivary Gland Cancers. Available online: https://clinicaltrials.gov/ct2/show/NCT04209660 (accessed on 20 December 2021).
41. Li, Z.; Tang, P.; Xu, Z. Clinico-pathological significance of microvessel density and vascular endothelial growth factor expression in adenoid cystic carcinoma of salivary glands. Zhonghua Kou Qiang Yi Xue Za Zhi 2001, 36, 212–214.
42. Park, S.; Nam, S.J.; Keam, B.; Kim, T.M.; Jeon, Y.K.; Lee, S.-H.; Hah, J.H.; Kwon, T.-K.; Kim, N.-W.; Sung, M.-W.; et al. VEGF and Ki-67 Overexpression in Predicting Poor Overall Survival in Adenoid Cystic Carcinoma. Cancer Res. Treat. 2016, 48, 518–526.
43. Kimi, K.; Ohki, K.; Kumamoto, H.; Kondo, M.; Taniguchi, Y.; Tanigami, A.; Ooya, K. Immunohistochemical and genetic analysis of mandibular cysts in heterozygous ptc knockout mice. J. Oral Pathol. Med. 2003, 32, 314.
44. Guigay, J.; Fayette, J.; Even, C.; Cupissol, D.; Rolland, F.; Peyrade, F.; Laguerre, B.; Le Tourneau, C.; Zanetta, S.; Le Moal, L.B.; 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, 6086.
45. Misiorek, J.O.; Przybyszewska-Podstawka, A.; Kałafut, J.; Paziewska, B.; Rolle, K.; Rivero-Müller, A.; Nees, M. Context Matters: NOTCH Signatures and Pathway in Cancer Progression and Metastasis. Cells 2021, 10, 94.
46. Van Weert, S.; Reinhard, R.; Bloemena, E.; Buter, J.; Witte, B.I.; Vergeer, M.R.; Leemans, C.R. Differences in patterns of survival in metastatic adenoid cystic carcinoma of the head and neck. Head Neck 2016, 39, 456–463.
47. Ferrarotto, R.; Mitani, Y.; Diao, L.; Guijarro, I.; Wang, J.; Zweidler-McKay, P.; Bell, D.; William, W.N., Jr.; Glisson, B.S.; Wick, M.J.; et al. Activating NOTCH1 Mutations Define a Distinct Subgroup of Patients With Adenoid Cystic Carcinoma Who Have Poor Prognosis, Propensity to Bone and Liver Metastasis, and Potential Responsiveness to Notch1 Inhibitors. J. Clin. Oncol. 2017, 35, 352–360.
48. Chintakuntlawar, A.V.; Okuno, S.H.; Price, K.A.R. Genomic testing may offer therapeutic opportunity in salivary gland cancers. J. Clin. Oncol. 2015, 33, e17053.

49. Su, B.-H.; Qu, J.; Song, M.; Huang, X.-Y.; Hu, X.-M.; Xie, J.; Zhao, Y.; Ding, L.-C.; She, L.; Chen, J.; et al. NOTCH1 signaling contributes to cell growth, anti-apoptosis and metastasis in salivary adenoid cystic carcinoma. Oncotarget 2014, 5, 6885–6895.
50. Ferrarotto, R.; Heymach, J.V. Taking it up a NOTCH: A novel subgroup of ACC is identified. Oncotarget 2017, 8, 81725–81726.
51. Ferrarotto, R.; Eckhardt, G.; Patnaik, A.; LoRusso, P.; Faoro, L.; Heymach, J.; Kapoun, A.; Xu, L.; Munster, P. A phase I dose-escalation and dose-expansion study of brontictuzumab in subjects with selected solid tumors. Ann. Oncol. 2018, 29, 1561–1568.
52. Di Villeneuve, L.; Souza, I.L.; Tolentino, F.D.S.; Ferrarotto, R.; Schvartsman, G. Salivary Gland Carcinoma: Novel Targets to Overcome Treatment Resistance in Advanced Disease. Front. Oncol. 2020, 10, 580141.
53. Miranda, E.L.; Stathis, A.; Hess, D.; Racca, F.; Quon, D.; Rodon, J.; Gadea, O.S.S.; Garcia, J.M.P.; Nuciforo, P.; Vivancos, A.; et al. Phase 1 study of CB-103, a novel first-in-class inhibitor of the CSL-NICD gene transcription factor complex in human cancers. J. Clin. Oncol. 2021, 39, 3020.
54. Ayala Pharmaceuticals, I. A Study of AL101 in Patients with Adenoid Cystic Carcinoma (ACC) Bearing Activating Notch Mutations (ACCURACY). Available online: https://clinicaltrials.gov/ct2/show/NCT03691207 (accessed on 21 December 2021).
55. Valimaa, H.; Savolainen, S.; Soukka, T.; Silvoniemi, P.; Makela, S.; Kujari, H.; Gustafsson, J.-A.; Laine, M. Estrogen receptor-beta is the predominant estrogen receptor subtype in human oral epithelium and salivary glands. J. Endocrinol. 2004, 180, 55–62.
56. Marques, Y.M.F.S.; Giudice, F.S.; Freitas, V.M.; e Lima, M.D.C.C.A.; Hunter, K.D.; Speight, P.M.; Sousa, S.C.O.M.D. Oestrogen receptor β in adenoid cystic carcinoma of salivary glands. Histopathology 2012, 60, 609–616.
57. Martelli, A.M.; Evangelisti, C.; Chappell, W.; Abrams, S.L.; Bäsecke, J.; Stivala, F.; Donia, M.; Fagone, P.; Nicoletti, F.; Libra, M.; et al. Targeting the translational apparatus to improve leukemia therapy: Roles of the PI3K/PTEN/Akt/mTOR pathway. Leukemia 2011, 25, 1064–1079.
58. Kim, D.-W.; Oh, D.-Y.; Shin, S.H.; Kang, J.H.; Cho, B.C.; Chung, J.-S.; Kim, H.; Park, K.U.; Kwon, J.H.; Han, J.-Y.; et al. A multicenter phase II study of everolimus in patients with progressive unresectable adenoid cystic carcinoma. BMC Cancer 2014, 14, 795.
59. Harvey, R.D.; Carthon, B.C.; Lewis, C.; Hossain, M.S.; Zhang, C.; Chen, Z.; Harris, W.B.; Alese, O.B.; Shaib, W.; Bilen, M.A.; et al. Phase 1 safety and pharmacodynamic study of lenalidomide combined with everolimus in patients with advanced solid malignancies with efficacy signal in adenoid cystic carcinoma. Br. J. Cancer 2020, 123, 1228–1234.

60. Liu, H.; Du, L.; Wang, R.; Wei, C.; Liu, B.; Zhu, L.; Liu, P.; Liu, Q.; Li, J.; Lu, S.-L.; et al. High frequency of loss of PTEN expression in human solid salivary adenoid cystic carcinoma and its implication for targeted therapy. Oncotarget 2015, 6, 11477–11491.
61. Yu, G.-T.; Bu, L.-L.; Zhao, Y.-Y.; Liu, B.; Zhang, W.-F.; Zhao, Y.-F.; Zhang, L.; Sun, Z.-J. Inhibition of mTOR reduce Stat3 and PAI related angiogenesis in salivary gland adenoid cystic carcinoma. Am. J. Cancer Res. 2014, 4, 764–775.