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Evaluating new treatments for anaplastic thyroid cancer

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Abstract:	Anaplastic thyroid cancer (ATC) is one of the most lethal diseases known to humans with a median survival of 5 months. The American Thyroid Association (ATA) recently published guidelines for the treatment of this dreadful thyroid malignancy. When the tumor is felt to be resectable, the treatment consists of surgery followed by (chemo)radiotherapy, but when the tumor is unresectable, the different treatments are aimed at trying to achieve a response that may reduce the tumor to resectable proportions, or at least, slow its growth and spread in order to extend survival. Recent

	advances are directed towards individualized treatment of patients depending on the genetic profile of the primary tumor and its metastases. In this article we review the latest published results and ongoing clinical trials, in an attempt to give an overview of the various treatment approaches currently being investigated.
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Highlights

- Anaplastic thyroid cancer is one of the most lethal diseases known to humans with a median survival of 5 months.
- Personalized medicine is probably the key for improving the outcome.
- Dabrafenib and trametinib for tumors harboring the BRAF V600E mutation has provided a useful treatment option.
- Combinations of drugs acting on different molecular pathways is the last attempt for fighting this cancer.

"Evaluating new treatments for anaplastic thyroid cancer"

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“Evaluating new treatments for anaplastic thyroid cancer”

Abstract

Anaplastic thyroid cancer (ATC) is one of the most lethal diseases known to humans with a median survival of 5 months. The American Thyroid Association (ATA) recently published guidelines for the treatment of this dreadful thyroid malignancy. When the tumor is felt to be resectable, the treatment consists of surgery followed by (chemo)radiotherapy, but when the tumor is unresectable, the different treatments are aimed at trying to achieve a response that may reduce the tumor to resectable proportions, or at least, slow its growth and spread in order to extend survival. Recent advances are directed towards individualized treatment of patients depending on the genetic profile of the primary tumor and its metastases. In this article we review the latest published results and ongoing clinical trials, in an attempt to give an overview of the various treatment approaches currently being investigated.

Key words: Anaplastic Thyroid Cancer, Treatment, Tyrosine-kinase Inhibitors, Immunotherapy, Immune Checkpoint Inhibitors, Targeted Therapy.

Introduction

Anaplastic thyroid cancer (ATC) is the most aggressive and lethal disease of the thyroid gland, with a reported median survival of 5 months and 1-year survival rate of 20%[1]. While accounting for less than 2% of thyroid malignancies, ATC is responsible for 25% of all thyroid cancer-related deaths[2,3]. Typically it presents as a rapidly growing thyroid mass, with local compression symptoms (neck pain, dysphagia and stridor), and generally affecting patients in their sixth and seventh decades of life[4]. ATC is composed of undifferentiated thyroid cells and typically presents at an advanced stage at the time of diagnosis[5]. ATC may evolve from a differentiated or poorly differentiated thyroid cancer, and while maintaining the genomic profile of the original tumor, however ATC does not usually exhibit histologic characteristics of follicular cells[6,7]. Poorly differentiated thyroid cancer and the tall cell variant of papillary thyroid cancer were the most common subtypes found associated with these mixed/transformed ATC sub-types in the Memorial Sloan Kettering Cancer Center series[8].

In 2021, the American Thyroid Association (ATA) published the most recent guidelines for management of patients with ATC[3], recommending total thyroidectomy for patients with localized tumors confined to the thyroid gland in whom a complete resection is feasible, followed by (chemo)radiotherapy. For more advanced disease, the treatment must be individualized according to the patient's general medical condition, and his/her goals of care.

In 2018, Janz et al. assessed the incidence of ATC using the Surveillance Epidemiology and End Results (SEER) database from 1973 to 2014, identifying 1527 patients in the database and a noted increased incidence from 0.2 per 1,000,000 people in 1973 to 1.2 per 1,000,000 people in 2014[9]. This finding has not been associated with a change in survival. Median disease specific survival (DSS) did not improve, being 4

months (95% CI: 2.26-5.74) from 1995 to 1999 and remaining 4 months (95% CI: 3.26-4.74) in the period from 2010 to 2014. Patients who were not treated surgically had a DSS of 2 months (95% CI: 1.65-2.35) compared to 6 months (95% CI: 3.91-8.09) for patients treated by subtotal or near total thyroidectomy and 10 months (95% CI: 7.70-12.30) for those who underwent a total thyroidectomy. The authors point out that this increase in incidence, could be explained by the expansion of the SEER database and because of the population of the United States is increasing. Furthermore, the increase could be due to improved diagnostic guidelines for healthcare providers.

Nevertheless, in a single-institution cohort study of 479 patients with ATC spanning nearly 20 years, 1- and 2-year survival significantly increased from 35% and 18% in the 2000-2013 time period (n = 227) to 47% and 25% during 2014-2016 (n = 100), and 59% and 42% in the 2017-2019 time period (n = 152), respectively. The determining differential fact was that more patients received targeted therapy in the 2017-2019 group vs the 2000-2013 and 2014-2016 groups (61%, 9%, and 43%, respectively). Median OS for patients treated with targeted therapy, regardless of their grouping, was 1.31 years (15.7 months) (95% CI, 1.07-1.99 years) compared with 0.63 years (7.6 months) (95% CI, 0.52-0.72 years) in patients not having received any targeted therapy[10].

In a report by de Rider et al. [11] all patients with ATC between 1989 and 2016 were identified from the Netherlands Cancer Registry, concluding that the incidence has increased slightly in the last 30 years but there is a subgroup of patients with longer survival, and they correspond to cases with limited disease and who underwent a combination of two or three treatment modalities.

In light of these disappointing results, it is the purpose of this review to present the current therapeutic land-scape of this challenging disease. We also present the results

from recent published trials over the last five years and the summarize currently active clinical trials.

Treatment options

Given the unchanged prognosis of these tumors in the past few decades, a focus on the biology and the genetic profile of ATC is necessary to devise new therapeutic strategies that impact key elements in the oncogenetic pathway to improve patient outcome. Along those lines, the most commonly identified BRAF V600E mutation analysis should be performed within the context of next-generation sequencing [7].

Currently, targeting a number of pathways appear to offer some promise including multitarget tyrosine-kinase inhibitors (TKI), epidermal growth factor receptor (EGFR), BRAF, mammalian target of rapamycin (mTOR) inhibitors, targeted peroxisome proliferator activated receptor-gamma (PPARγ) ligand molecules, vascular disruptor molecules, such as vascular endothelial growth factor receptor (VEGFR) inhibitor and immune checkpoint inhibitor targeting programmed cell-death 1 (PD-1), and its ligands (PD-L1). Each strategy has a distinct anti-tumor mechanism as well as specific side effects, which must be taken into account when considering therapeutic options. In the following sections we will review these targeted agents relying on studies published between 2016 and 2021.

1) Targeted therapy

Multitargeted TKI

Lenvatinib

Lenvatinib is an oral multitarget TKI that inhibits VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor-α and RET and KIT proto-oncogenes[12].

We identified two clinical trials in the last 5 years using lenvatinib for advanced thyroid cancer. Takahashi et al.[13] published in 2019 a phase II study including 51 patients who received lenvatinib in advanced thyroid cancer. Seventeen had ATC, with a mean age of 65 years. Eleven of the patients were women. 82% of the patients had previously undergone surgery, 41% chemotherapy and 53% radiotherapy. All patients had treatment-related adverse events (AEs), 88% of which were grade 3 or 4. Serious AEs were deemed related to lenvatinib in 13 patients, with 3 deaths, 1 life threatening AE and 13 patients requiring inpatient hospitalization or prolongation of existing hospitalization. The most common side effects of this drug were hypertension and decreased appetite in 82% of the patients, as well as fatigue, proteinuria, and nausea in 59%. Additional adverse reactions included palmar-plantar erythrodysesthesia syndrome or stomatitis that were seen in 47% of patients. The objective response rate was 24%, the disease control rate 94%, and the overall clinical benefit 71%, while most of them were classified as having stable disease > 11 weeks. The median progression-free survival (PFS) for the ATC group was 7.4 months. Wirth et al.[14] published an open-label, single-arm, multicenter, phase II trial of lenvatinib for patients with ATC: Thirty-four patients were enrolled, all over the age of 65 years, 62% females and 71% had prior anticancer therapy, 71% surgery and 65% radiation therapy. More than half of the patients experienced tumor shrinkage (partial response and stable disease), but the confirmed overall response rate (ORR) was 0% as there were no patients with a confirmed partial or complete response in the interim analysis set. Therefore, the study was halted based on the prespecified criteria for futility, as the minimum ORR threshold of 15% was not met. The median PFS was 2.6 months (95% CI, 1.4 - 2.8); while the median overall survival (OS) was 3.2 months (95% CI, 2.8 - 8.2). The most common treatment-related AEs were hypertension (56%), decreased appetite (29%), fatigue (29%), and stomatitis (29%).

Sorafenib

Sorafenib inhibits vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3; platelet-derived growth factor receptor (PDGFR); mitogen-activated protein kinase (MAPK) members BRAF and RET; chimeric protein RET/PTC; and c-KIT[15].

In 2017, Ito et al.[16] conducted an uncontrolled, open-label, multicenter, single-arm, phase II clinical trial to evaluate sorafenib in Japanese patients with medullary thyroid cancer and ATC. Eighteen patients were included of which 10 had ATC. The most common drug-related AEs in patients with ATC were palmar-plantar erythrodysesthesia (50%), rash (40%), hypertension (50%), and weight loss (50%). Median PFS was 2.8 months (95% CI 0.7–5.6), and median OS was 5.0 months (95% CI 0.7–5.7). Objective response (complete and partial response) and disease control rates (stable disease) were 0% and 40%, respectively. They concluded that sorafenib did not seem to be effective for ATC.

Sherman et al.[17] evaluated the combination of sorafenib and temsirolimus in patients deemed to have radioactive iodine-refractory thyroid cancer in a phase II study. Temsirolimus is an inhibitor of mTOR, and it binds to an abundant intracellular protein, FKBP-12, forming a complex that inhibits mTOR complex 1 (mTORC1) signaling[18]. Interrupting mTOR signaling inhibits the protein synthesis regulating cell cycle progression and angiogenesis[19,20]. mTORC1 activity in the thyroid cells. It is required for the proliferative effects of thyroid stimulating hormone (TSH) in vitro and in vivo[21], and its inhibition suppresses growth of thyroid cancer cell lines in vitro[22]. There were 36 patients treated. One of the 2 ATC patients had a partial response and was on study for 6.9 months. This patient had been previously treated with paclitaxel, pazopanib, and radiation therapy and was 81 years of age. The most common grade 3 and 4 toxicities associated with these drugs included hyperglycemia, fatigue, anemia, and oral mucositis.

Sunitinib

Sunitinib is an oral multitargeted TKI against VEGFRs (1 and 2), PDGFRs (α and β), c KIT, FMS-like tyrosine kinase-3 (FLT3), glial cell-line derived neurotrophic factor receptor (RET) and the receptor of macrophage colony stimulating factor (CSF1R)[23]. Ravaud et al.[24] published in 2017 the data from the THYSU study, which investigated the use of Sunitinib in locally uncontrolled recurrent disease or advanced metastases in thyroid cancer. They included 71 patients (45 differentiated follicular carcinomas or ATC and 26 medullary carcinomas). There were 4 ATC patients treated with sunitinib, and these patients died at 3.3, 3.5, 7.8 and 26.5 months. Asthenia was the most frequent side effect in 83.1% of patients including 25.4% patients with grade 3 and 1.4% with grade 4 fatigue. Of all patients, 14.1% had a cardiac event. Nine unexpected side effects were reported, of which, 5 were fatal. The authors concluded that the treatment with sunitinib is effective in medullary and differentiated thyroid cancer but did not seem to improve the natural history of the disease in ATC patients.

Anti-BRAF molecules

Dabrafenib/Trametinib

BRAF inhibitors (in combination with MEK inhibitors) can be effective in malignancies with a BRAF V600E mutation. As 40-70% of ATC carry such mutation[25,26], BRAF/MEK inhibitory treatment is of interest. Dabrafenib is a BRAFV600E kinase signaling inhibitor, whereas trametinib is a kinase inhibitor that blocks MEK, which is downstream from BRAF in the MAPK pathway. BRAF/MEK inhibition is given in combination to overcome early resistance to BRAF inhibitors [27,28]. This combination treatment has been tested in a clinical trial with hopeful results. In 2018, Subbiah et al.[29] completed a study of 16 patients, 15 of which had BRAF

V600E mutated tumors. The median age was 72 years, 63% were female, and 63% were of Asian heritage. Prior treatments included surgery (88%), external beam radiotherapy (81%), and chemotherapy (38%). Median duration of follow-up for the ATC cohort was 47 weeks (range 4 - 120). The confirmed overall response rate was 69% (95% CI, 41% - 89%), with complete response in 1 patient and partial response in 10 patients. The most common AEs were fatigue (38%), pyrexia (37%), and nausea (35%). With the combination of BRAF and MEK inhibition resulting in a promising clinical activity, this approach is now approved in the management of BRAF positive ATC.

In 2019, Wang et al.[30] published a case series using this treatment in 6 patients that were treated pre-operatively with neoadjuvant dabrafenib plus trametinib. Thereafter they underwent a surgical resection of the tumor and adjuvant chemoradiation (3 patients also received pembrolizumab). Remarkably, complete surgical resection was achieved in all cases. OS at 6 and 12 months were 100% and 83%, respectively. The locoregional control rate was 100% and 2 patients died of distant metastases without evidence of locoregional disease at 8 and 14 months from diagnosis. The remaining 4 patients had no evidence of disease at last follow-up (median: 16.5 months, range: 7.8–26.0 months). These results open the question of pre-operative (Induction) therapy as a possible valid option in the management of resectable disease.

Anti-mTOR molecules

Everolimus

Constitutive activation of the phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR pathway has been observed in thyroid cancer pathogenesis[7]. Everolimus is a Sirolimus-derived mTOR inhibitor. Administering everolimus to different ATC cell lines that previously had shown resistance to gefitinib ,showed a significant growth inhibition[31].

Schneider et al.[32] included 28 patients (7 with ATC) in a nonrandomized, open-label, multicenter, single-arm phase II trial, but the results were disappointing, with none of the patients responding to the treatment. The most frequent AEs were anemia and cough, each occurring in 64% of the patients, and time until death varied from 5 to 53 weeks. The authors concluded that everolimus does not have a role in ATC treatment.

Hanna et al.[33] conducted a single-arm, multi-institutional phase II study of patients with radioactive iodine-refractory thyroid cancer including 7 patients with ATC. One patient achieved a near-complete response, one had stable disease for 26 months and no evidence of progression prior to death (from congestive heart failure), while 4 progressed within 3 months of study entry. The last patient was unevaluable. All patients with a significant response to treatment had demonstrated mutations directly linked to mTOR activation. The median PFS of the ATC patients was 2.8 months (median OS, 8.9 months).

2) Immunotherapy

Checkpoint inhibitor drugs targeting PD-1 or PD-L1

Spartalizumab

Macrophages and T-cells express a glycoprotein called programmed cell-death 1 (PD-1), and when its ligands (PD-L1 or PD-L2) bind to it, they inhibit cytotoxic T-cell immune response that leads to an immune escape of the cells that express these ligands. This glycoprotein is found in more than 65% of ATC cells[34–36].

Spartalizumab is a humanized immunoglobulin 4 monoclonal antibody that binds PD-1 with sub nanomolar activity, blocking interaction with PDL1 and PD-L2[37]. In 2020, Capdevila et al.[38] published a phase II study on 42 patients with ATC, 2 of them without tumor tissue available for central pathology review. The commonest AEs were

diarrhea (12%), pruritus (12%), fatigue (7%), and pyrexia (7%). The overall response rate was 19%, including 3 patients with a complete response and 5 with a partial response. Twenty-eight of the 40 patients with available biopsy material showed tumors that expressed PD-L1, and response rates were higher in PD-L1–positive (29%) versus PD-L1–negative (0%) patients. The highest rate of response (35%) was observed in patients with PD-L1 ≥ 50%. Responses were seen in both BRAF-nonmutant and BRAF-mutant patients and were durable, with a 1-year survival of 52.1% in the PD-L1–positive population. This study demonstrated the responsiveness of ATC to PD-1 blockade.

Pembrolizumab

Pembrolizumab is a selective anti-PD-1 monoclonal antibody. It was used in combination with chemoradiotherapy by Chintakuntlawar et al.[34] in a phase II study on 3 ATC patients with unresectable disease. After an initial tumor response, all patients died in less than 6 months, with a median OS of 2.76 months. Iyer et al.[39] studied the use of pembrolizumab in combination with TKI (lenvatinib, trametinib +/-dabrafenib) at the time of progression on TKI alone. Twelve patients were treated: 42% had partial response, 33% had stable disease and 25% had progressive disease. Clinical benefit (partial response and stable disease) was seen in 75% patients. Fatigue, anemia, and hypertension were the most common AEs encountered. Median OS from the start of TKI was 10.43 months (95% CI = 6.02, 14.83, range 5.4–40 months). Median OS and PFS from the addition of pembrolizumab were 6.93 months (95% CI, 1.7 - 12.15; range 3–15.9 months) and 2.96 months (95% CI, 2.2 - 3.7; range 0.57–13.14 months), respectively. The authors conclude that pembrolizumab may be an effective therapy added to TKI at the time of progression on these drugs.

Other therapies – Current trials

A search for the recent clinical trials available (https://clinicaltrials.gov, date: 4/1/2022), resulted in 72 ongoing studies with ATC patients. We found 9 clinical trials with preliminary unpublished results (Table 1) and 21 active trials with results pending (Table 2). When analyzing the clinical trials with available preliminary results, there are 4 where a molecular compound is used in addition to chemotherapy (i.e. Crolibulin+Cisplatin, Combretastatin+Paclitaxel/Carboplatin...). In general, no clear improvement of the poor prognosis of ATC was observed. However, among the trials without results, we note a large number of drugs (21 studies with 25 drugs) that are being analyzed, indicating the great effort that is being undertaken to improve the treatment of ATC. When analyzing ongoing studies, there is a clear trend towards the use of multiple therapies to target different pathways simultaneously (TKI+anti PD1 or PD-L1, anti BRAF+MEK inhibitor+anti PD1 or PD-L1…).

Discussion

ATC is the most aggressive and dreaded thyroid malignancy, and when resectable, the preferred treatment is surgery followed by definitive radiation with or without chemotherapy (taxane monotherapy or with platin or anthracycline)[3]. ATC can arise as a result of terminal de-differentiation of well-differentiated thyroid cancer, it can develop in a preexisting goiter (≥80% of ATC come from a longstanding history of multinodular thyroid disease)[40] or may develop de novo[41]. Some studies confirmed the presence of a well-differentiated thyroid cancer within ATC tumors, which lead to the hypothesis of a post malignant de-differentiation. This is controversial as, only a very small number of differentiated carcinomas progress to ATC[42,43]. ATC tumorigenesis may be a multistep process with a biological transformation (synchronous or metachronous) from differentiated thyroid cancer to ATC[44]. The recent understanding of the genomic profile of this disease, has led to impressive improvement in patient outcomes using

specific targeted agents. Patients are currently selected for multimodal treatment at large academic centers. Management of this disease remains however very challenging in non-referral institutions who see few ATC patients. In ATC one can find mutations of BRAF and RAS[45], PI3K/Akt pathway[46], PIK3CA[47], p53 and B-Catenin (CTNNB1)[48,49]… and investigations are ongoing trying to block these pathways in order to achieve a favorable tumor response.

In the most recent ATA guidelines for ATC, the authors suggested in their Recommendation 4, that assessment of BRAF V600E mutation should be performed by immunohistochemistry and confirmed by molecular testing. Recommendation 5 proposes that molecular profiling should be performed at diagnosis as well as at the time of progression[3]. Initial treatment of stage IVB disease, is chemoradiation. In stage IVB, if chemoradiation is not feasible for the patient, and in the presence of BRAFV600E mutations, Dabrafenib and Trametinib, a combination treatment, approved by the U.S. Food and Drug Administration (FDA) for this indication, may be used. In $BRAF^{wt}$ tumors, another genetic alteration such as ALK, NTRK or RET fusions suggest targeted therapy should be considered, depending on the availability of such treatment options. More clinical data is however needed to assess the role of these agents in unresectable disease. In addition, a rapid genomic analysis remains a major challenge for small non-referral centers and its use may be counter-productive by delaying therapy. In cases of excellent tumor response, subsequent surgery, and definitive radiotherapy or chemoradiotherapy, should be undertaken. In cases of stage IVC disease, a similar strategy for targeted therapy can be followed. In addition, participation in immunotherapy trials may be helpful for patients with tumors with high PD-L1 expression.

Different TKIs, such as lenvatinib, sorafenib, and others like imatinib and pazopanib have also been used for the treatment of ATC. All of them have shown limited

activity against ATC in terms of PFS or OS. They are used because they target trans-membrane tyrosine kinase receptors that initiate signaling through the MAP kinase pathway. In the same signaling pathway we can use inhibitors of RAS, RET, RAF, and MEK kinases[50].

As stated above, anti-BRAF molecules are recommended by the ATA for treatment of unresectable ATC with the BRAFV600E mutation that has been identified as the driver mutation in 45% of ATC cases[25]. BRAF inhibition resulted in diminished phosphorylation of ERK and MEK kinases in the mitogen-activated protein kinase (MAPK) signaling cascade[51,52]. Dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor) is a promising new combination targeted therapy for patients with BRAF V600E–mutated ATC, demonstrating a high overall response rate, prolonged duration of response, and survival with manageable toxicity[29]. Furthermore, in the above cited study by Maniakas et al.[10], surgical resection following neoadjuvant therapy was completed in 23 patients (15%) in the 2017-2019 group compared with none in the 2000-2013 and 2014-2016 groups. In patients who received BRAF-directed therapy (most of them with dabrafenib/trametinib), those who underwent surgery following neoadjuvant therapy ($n = 20$) had statistically significant improvement in median OS compared with those who did not. Nevertheless, similar to experience with other tumors, the emergence of RAS mutations appears to act as a mechanism of resistance to BRAF inhibitors in thyroid cancers[53]. Other BRAFV600E kinase signaling inhibitors studied in prospective clinical trials include vemurafenib/cobimetinib, followed by atezolizumab. From 10 patients with surgically unresectable disease enrolled in a cohort, 6 patients underwent complete resection of primary or residual tumor[54].

Anti-mTOR molecules have been used in an attempt to treat these tumors. Activation of the mTOR serine/threonine protein kinase has been reported in a variety of

malignant tumors with an estimated 70% of mTOR upregulation[55]. Everolimus (RAD001) is an orally active derivative of rapamycin, targeting mTOR. This drug exerts its activity through high-affinity interaction with an intracellular receptor protein, the immunophilin FKBP12, and subsequently interacts with the mTOR protein kinase, inhibiting downstream signaling events involved in regulation of the G1- to S-phase transition[56]. The results in terms of their effectiveness are heterogeneous.

Checkpoint inhibitor drugs targeting PD-1 or PD-L1 represent the next frontier in treating ATC. T-cells express program cell death-receptor 1 (PD-1) on their surface, which interact with a ligand on normal tissues. Tumor cells express programmed cell death ligand 1 (PDL-1), and the interaction between receptor and ligand suppresses T-cell mediated cytotoxicity towards the thyroid tumor[57]. ATA guidelines for ATC suggested that in stage IVC patients with high PD-L1 expression, checkpoint (PD-L1, PD1) inhibitors can be considered as the first-line therapy in the absence of other targetable alterations or as subsequent therapy, preferably in the context of a clinical trial[3].

Conclusions

Treatment of ATC is based on a combination of surgery, if possible, with (chemo)radiotherapy, but prognosis remains poor. Recent attempts to improve the prognosis of these tumors are moving towards personalized medicine, basing the treatment decision on the specific genetic profile of the individual tumor. The positive results of dabrafenib and trametinib for ATC harboring the BRAF V600E mutation has provided a useful treatment option. For the other genetic profiles, different drugs are available and can be used to individualize the treatment, probably using some drugs together. Combinations of drugs act on different molecular pathways and achieve inhibition at separate areas. With new targeted therapies the average survival has

improved considerably and death from local disease progression or airway compromise is less likely with improvement in quality of life. Unfortunately, the results are still poor in terms of survival. It is necessary to continue exploring novel therapies for ATC.

Table 1: Clinical trials on ATC with results available.

				No. patients [NCT number]	**Response**	**More common AE**
Clinical trials (with results)	Inmunotherapy	PD-1 and PD-L1 inhibitors	Pembrolizumab	6 (5♀-1♂) [NCT02688608]	3 PR 1 SD 1 PD 1 Lost	Dyspnea (50%) Respiratory failure (33.3%) Rash (33.3%) Mucositis (33.3%)
	Vascular disruptors		Combretastatin (CA4P)	55 CA4P+CT (25♀-30♂) 25 CT (18♀-7♂) [NCT00507429]	CA4P+CT: 5.2 months CT: 4 months	Bronchitis (9.8%) Febrile Neutropenia (5.8%)
			Crolibulin	27 Crolibulin+Cisplatin (7♀-20♂) [NCT01240590]	NA	Gastrointestinal and respiratory disorders (16.67%)
	Tyrosine-kinase inhibitors		Lenvatinib	34 (21♀-13♂) [NCT02657369]	PFS: 2.6 months OS: 3.2 months 27 deaths	Dyspnea (11.76%) Pulmonary embolism (8.82%)
			Sorafenib	20 (7♀-13♂) [NCT00126568]	2 PR 5 SD	Dyspnea (10%)

				11 PD PFS: 1.9 months OS: 3.9 months	
		Imatinib	11 (5♀-6♂) [NCT00115739]	2 PR 4 SD 3 Lost SR at 6 months: 46%	Anemia (54.5%), hypertension (53.3%), nauseas (45.45%), fatigue and edema (63.6%)
		Pazopanib	15 (10♀-5♂) [NCT00625846]	NA	Fatigue (80%), anorexia (53.3%), diarrhea (46.67%), nausea (40%)
	PPARγ agonist	CS7017	15 CS7017 + CT (10♀-5♂) [NCT00603941]	1 PR 8 SD 4 PD 2 unknown	Anaphylatic reaction, infections, dysphagia, dyspnea

	Inhibitor of HDAC and PI3K	CUDC-907	7 [4 ATC (2♀-2♂)] [NCT03002623]	Median survival after therapy: 127 days	Gastrointestinal and general disorders

AE: Adverse events, **CT**: Chemotherapy, **CRT**: Chemoradiotherapy, **DCC**: Disease control rate, **NA**: Not available, **NTC**: Clinicaltrials.gov identifier, **ORR**: Overall response rate, **PD**: Progressive disease, **PR**: Partial response, **SD**: Stable disease, **SR**: Survival rate.

Table 2: Drugs used in active clinical trials without results available yet.

			Drug **[NTC]**
Active clinical trials (no results available)	MEK inhibitors		Trametinib [NCT03085056] [NCT04739566] [NCT04675710] [NCT03975231]
			Cobimetinib [NCT03181100]
	Immunotherapy	PD-1 and PD-L1 inhibitors	Durvalumab [NCT03122496]
			Cemiplimab [NCT04238624]
			Atezolizumab [NCT03181100] [NCT04400474]
			Pembrolizumab [NCT04675710] [NCT05119296]

			[NCT05059470]
			Tislelizumab [NCT04579757]
			Nivolumab [NCT03246958]
		CTLA-4 inhibitors	Tremelimumab [NCT03122496]
			Ipilimumab [NCT03246958]
	mTOR inhibitor	MLN0128 [NCT02244463]	
	PPARγ agonist	Efatutazone [NCT02152137]	
	Tyrosine-kinase inhibitors	Pazopanib [NCT01236547]	
		Surufatinib [NCT04579757]	
		Selpercatinib [NCT04759911]	

		Cabozantinib [NCT04400474] [NCT02041260]
	CDK inhibitors	Abemaciclib [NCT04552769]
		CDK-002 [NCT04592484]
	IL-2	Aldesleukin [NCT03449108]
	Vascular disruptors	Bevacizumab [NCT03181100]
	Anti-BRAF molecules	HLX208 [NCT05102292]
		Vemurafenib [NCT03181100]
		Dabrafenib [NCT04739566] [NCT04675710] [NCT03975231]

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