REVIEW

Anaplastic thyroid carcinoma: advances in molecular profiling and targeted therapy

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Purpose of review
Anaplastic thyroid carcinomas (ATCs) are rare cancers with a globally very poor prognosis, because of their immensely aggressive behaviour, resulting in predominantly advanced stage of disease at diagnosis. Response to available therapies is still disappointing. Aim of the present review is to illustrate the diverse new strategies under investigation, to improve the poor outcome of these patients.

Recent findings
Applying molecular analysis in ATC is unravelling potentially actionable targets of therapy. If a mutation of *BRAF V600E* is found, a combination of Dabrafenib and Trametinib is the recommended treatment. In the presence of another druggable mutation, a specific targeted therapy may be proposed. In the absence of druggable mutations, immunotherapy is an alternative approach, especially in case of significant PD-L1 expression.

Summary
The molecular profiling of tumour samples is elucidating the genetic alterations involved in ATC development, and new preclinical models are under study to define innovative approaches for individualized treatment of such patients. Hopefully this approach could improve ATC prognosis.

Keywords
anaplastic thyroid carcinoma, *BRAF*, immunotherapy, targeted therapy

INTRODUCTION

Anaplastic thyroid carcinomas (ATCs) originate from follicular thyroid cells and generate the highest mortality rate, while representing a minor proportion of all thyroid cancers [1]. These tumours present in fact an extremely aggressive course, being usually diagnosed at an advanced stage, with a large tumour mass, extrathyroidal extension and often distant metastases. A treatment with curative intent is, therefore, impossible and the prognosis is very poor, with a median survival of approximately 4–5 months after diagnosis and a 1-year survival rate of 10–20% [2]. For all these reasons, the most recently released guidelines (ESMO, ATA) [3▪▪,4] have pointed out the need for a multidisciplinary approach, to rapidly establish a treatment plan, involving surgeons, radiation oncologists, medical oncologists, endocrinologists, and pathologists. Moreover, because of the disappointing results with 'classic' chemotherapy (ChT), new strategies need to be defined. At the present stage of knowledge, the general agreement is all treatments should be personalized for individual ATC patients (ATA guidelines) and enrolment in clinical trials should preferably be considered for patients with good performance status. Palliative ChT may be proposed in the absence of other therapeutic options [3▪▪,4] and for patients not eligible for accessible therapeutics or clinical trials, best supportive care should be discussed (ESMO, ATA guidelines).

The present review will summarize:

(1) the results of the most recent preclinical studies concerning the identification of new molecular drivers and the clarification of the dedifferentiation mechanisms involved in ATC development;
(2) the emerging therapeutic approaches to ATC, in the context of precision medicine.

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KEY POINTS

- Anaplastic thyroid carcinomas (ATCs) are rare cancers with globally a very poor prognosis because of their predominantly advanced stage of disease at diagnosis, and their immensely aggressive behaviour.
- Cytotoxic chemotherapy has been the primary treatment for metastatic disease, but it is associated with very low response rates.
- The molecular profile of ATC includes mutations of the *TERT* promoter (associated with *BRAF* or *RAS* mutations) and *p53*, as well as targetable abnormalities (e.g. *NTRK* and *ALK* rearrangements). A next-generation sequencing analysis targeting cancer-associated genes should be performed if available.
- *BRAF* inhibitor dabrafenib with the *MEK* inhibitor trametinib should be the first-line therapy for advanced *BRAF V600E* mutated ATC patients if available.

PRECLINICAL DATA

Molecular profiling

Although the molecular drivers and the different steps leading to dedifferentiation associated with thyroid tumorigenesis started being unfolded more than a decade ago, limited data is available on the molecular profiling of ATC samples. A comprehensive review on the molecular studies applying next-generation sequencing (NGS) is presented in Table 1 [5–17,18▪]. Due to the methodological differences (number of genes screened, whether all coding region was screened or not, number of times resequenced), the detected frequencies may substantially differ among studies. The most frequent driver mutations are *BRAF* (v-raf murine sarcoma viral oncogene homolog B1) and *RAS* (rat sarcoma), occurring respectively in 14–56% and 13–44% of cases. They represent early mutations, also occurring in differentiated thyroid cancers (DTCs). By contrast, *RET/PTC* and *PAX8/PPARG* fusions are nearly not detected in ATCs. *RET* (rearranged during transfection) mutations may occur in up to 25% of cases. Increasingly reported genomic abnormalities include late mutations of the *TERT* promoter region (from 32% up to 80%, usually associated with *BRAF* or *RAS* mutations) and *p53*-mutated forms (from 27% up to 74%). Interestingly, NGS revealed the frequent co-occurrence of mutated *RAS* with mutations in *EIF1AX* (an essential eukaryotic translation initiation factor). The latter mutations showed to have a poor prognosis value in advanced tumours [6,11]. Alterations in genes coding for members of the *PI3K/AKT/mTOR* pathway can account for 20–40% of ATCs. As for mutations in receptor tyrosine kinases and in known tumour-suppressor genes, these have been infrequently found (in less than 10% of cases in most studies). Occasionally, other druggable abnormalities like *NTRK* and *ALK* rearrangements have been found [17]. Other genetic abnormalities involved in ATCs and revealed by NGS studies, are related to genes coding for subunits of the *SWI/SNF* chromatin remodelling complex, for histone modifiers and for mismatch repair proteins [6]. Finally, cell cycle dysregulation seen in ATCs may be attributed to abnormalities in the oncosuppressor *Retinoblastoma* (*RB*) pathway [7,10]. Regulation of the G1/S transition of the cell cycle is dependent on the activities of Cyclin D-CDK4/6 and Cyclin E-CDK2 complexes that inhibit the *RB* protein. Mutations or deletions of *CDKN2A* gene (coding for the p16 protein – a CDK4/6 inhibitor) and amplifications of *Cyclin E* gene may together affect 20–30% of cases [7,10].

Only mutations in *p53* seem to be significantly increased in ATCs compared with other advanced thyroid tumours [14,19,20]. Importantly, none of the genomic abnormalities found is specific for ATC [7,21] and the histopathologic diagnosis remains the gold standard for diagnosis [3▪▪]. Nevertheless, molecular profiling can help in differential diagnosis and to seek potential therapeutic targets for therapy.

The first analysis of ATC by single-cell RNA sequencing has also recently been reported [22▪▪], which confirmed previous findings about ATC progression from papillary thyroid cancer (PTC). By cell trajectory analysis, the authors showed that ATC and PTC had different progression routes, but a minor subset of PTC cells were similar and localized along the ATC progression, suggesting a common lineage. In this progression route, the main identified expressional changes were related to epithelial–mesenchymal transition, negative regulation of *p53*, markedly reduced thyroid differentiation and activation of *ERK* and *PI3K/mTOR* signalling. Interestingly, the characterization of the cellular composition of tumours suggested a highly immunosuppressive microenvironment in ATC, with dysfunctional markers associated to natural killer and T cells, enrichment on FOXP3- regulatory T cells, decreased M1/M2 macrophages ratio and immunosuppressive FAP+ fibroblasts and tumour-associated myeloid cells.

Preclinical models of anaplastic thyroid carcinomas

ATC being a rare entity, the establishment of preclinical models aimed at basic/translational studies is warranted. More than 30 ATC-derived cell lines have been until now validated [21], but their use as preclinical models presents several limitations (Fig. 1).

Table 1. Summary of the molecular alterations found in anaplastic thyroid carcinomas, reported in next-generation sequencing (NGS) studies analyzing more than 10 samples

Study		Kunstman *et al.* [5]	Landa *et al.* [6] and Pozdeyev *et al.* [7]	Tiedje *et al.* [8]	Bonhomme *et al.* [9]	Ravi *et al.* [10]	Yoo *et al.* [11]	Khan *et al.* [12]	Duan *et al.* [13]	Song *et al.* [14]	Lai *et al.* [15]	Iniguez-Ariza *et al.* [16]	Xu *et al.* [17]	Wang *et al.* [18▪]
Genes analysed		Complete protein-coding regions	287–465 (all exons)	18 (chosen exons)	50 (chosen exons)	Complete protein-coding regions	Complete exons and introns / 57 (chosen exons) + 12 fusion genes	182-315 (all exons) + 28 fusion genes	18 (chosen exons)	50 (chosen exons)	7 (chosen exons)	315 (all exons) + 28 fusion genes	324–468 (all exons)	46–50 (chosen exons)
Type of analysis		WES	TS	TS	TS	WES	WGS/TS	TS	TS	TS	TS	TS	TS	TS
Total of ATCs analysed		22	196	118	94	14	27	90	25	16	27	19	98	79-202
Type of samples		Frozen and FFPE	Frozen and FFPE	FFPE	FFPE	FFPE	Frozen and FFPE	Frozen and FFPE	FFPE	FFPE	FFPE	FFPE	FFPE	Frozen
Genes altered (%)														
BRAF		27	41	11	14	18	41	32	56	38	26	32	41	42
H-/K-/NRAS		27	27	20	43	18	44	29	28	13	41	21	24	22
EIF1AX		14	2	–	–	9	33	0	8	6	–	–	14	–
TERT		–	65	73[a]	54[a]	36	56	32	56	69	82	68	57	37
TP53		27	65	55	54	55	48	66	60	38	70	74	72	54
RET		5	0	8	2	0	0	2	–	25	–	11	0	–
RET/PTC fusions		–	0	–	–	0	0	2	0	–	–	0	2	–
PAX8-PPARG fusions		–	0	–	–	0	0	0	0	–	–	-	0	–
PI3K/AKT/mTOR	PIK3CA	10	14	12	6	18	11	12	44	0	15	16	15	13
	PTEN	0	11	–	9	18	7	13	12	0	–	16	13	7
	STK11	0	1	–	1	0	0	1	–	0	–	0	0	–
	MTOR	10	2	0	–	9	0	1	–	0	–	0	5	–
	TSC2	0	2	1	–	0	0	6	–	13	–	0	0	–
Receptor Tyrosine Kinases	ALK	0	0	0	1[b]	0	0[d]	2 / 0[d]	0	0	–	5	3	–
	EGFR	0	2	1	0	0	0	3	–	–	–	0	0	–
	ERBB2	5	1	2	1	0	0	3	–	–	–	21	0	–
	KIT	0	4	0	0	0	0	2	–	–	–	0	0	–
	MET	0	2	0	1	0	0[d]	2	–	–	–	0	0	–
	PDGFRA	0	3	1	0	0	0	2	–	6	–	5	0	–
Tumour supressors	NF1	10	9	–	–	9	0	12	–	0	–	16	12	10
	NF2	5	12	–	–	18	4	14	–	6	–	11	12	8
	ATM	5	4	–	4	27	4	7	–	0	–	21	7	3

Table 1 (*Continued*)

Study		Kunstman *et al.* [5]	Landa *et al.* [6] and Pozdeyev *et al.* [7]	Tiedje *et al.* [8]	Bonhomme *et al.* [9]	Ravi *et al.* [10]	Yoo *et al.* [11]	Khan *et al.* [12]	Duan *et al.* [13]	Song *et al.* [14]	Lai *et al.* [15]	Iniguez-Ariza *et al.* [16]	Xu *et al.* [17]	Wang *et al.* [18▪]
	MEN1	0	4	--	--	0	0	4	--	0	--	0	0	--
Cell cycle	RB1	0	7	1	1	18	0	6	--	0	--	11	9	4
	CDKN2A mutation or loss	--	22	17	3	9	22	32	--	--	--	11	25	4
	CCNE1 copy gains	--	4	--	--	29	--	4	--	--	--	11	--	--
SWI/SNF complex		5	18	--	2[c]	21	4	29	--	31	--	37	16	5
Histone modifications		5	19	--	--	18	15	6	--	50	--	0	13	--
Mismatch repair		14	6	--	--	9	0	3	--	13	--	5	8	--

FFPE, formalin-fixed paraffin-embedded; TS, targeted sequencing; WES, whole-exome sequencing; WGS, whole-genome sequencing.
[a]Sanger sequencing.
[b]Rearrangement by FISH detected in 1%.
[c]Only SMARCB1 analysed.
[d]Fusion genes searched.

Patient-derived tumour xenografts (PDTX) are obtained by implanting primary patient's ATC into an immunodeficient mouse (Fig. 1). They grow in a microenvironment that mimicks the patient's primary tumour site and maintain the genetic and epigenetic abnormalities found in the patient, thus representing an invaluable resource to investigate the patterns of tumour response/resistance to drugs.

Six new PDTX models have now been developed [23▪], accounting for a total of 13 available PDTX of ATC origin [24,25]. The same group has indeed published an illustrative example for the contribution of these models. They tested in cell lines by high-throughput screening 257 compounds, being able to narrow down and validate three compounds (docetaxel, Panobinostat, and pralatrexate) in two ATC PDTX [26▪].

Next-generation sequencing analysis has revealed that components of the *SWI/SNF* chromatin remodelling complex acting as epigenetic modifiers are involved in ATC. A recent study showed that in a *BRAF V600E*-driven context, the thyroid-specific homozygous loss of the SWI/SNF complex sub-units, such as Arid1a, Arid2, or Smarcb1 rapidly promoted transformation to poorly differentiated thyroid cancers (PDTCs) and/or ATCs in mice [27▪▪]. In these lesions, thyroid differentiation-related expression was attenuated. In addition, the SWI/SNF subunit loss impaired the rescue by *MAPK* inhibitors of redifferentiation/radioiodine uptake (notably because of failure in restoring membrane NIS expression).

CLINICAL DATA

Chemotherapy

Cytotoxic ChT has for a long time been the only treatment for metastatic disease, unfortunately leading to very low response rates. Recommended regimens include single-agent treatment with paclitaxel or doxorubicin, or combinations like carboplatin/paclitaxel or docetaxel/doxorubicin, administered weekly or every 3–4 weeks [28–30]. Doxorubicin is the only FDA-approved chemotherapy for ATC. Nevertheless, trials with doxorubicin in ATC generally analyse its use in combination with other treatment modalities like surgery and radiotherapy, making uncertain the assessment of its efficacy [31,32].

No clear data allowing second-line chemotherapy recommendation is available [3▪▪,4].

Tyrosine kinase inhibitors

Lenvatinib, a multikinase inhibitor of *VEGFR 1–3*, *FGFR 1–4*, *PDGFR*, *RET*, and *KIT*, is FDA-approved for differentiated thyroid cancer. Its efficacy in ATC

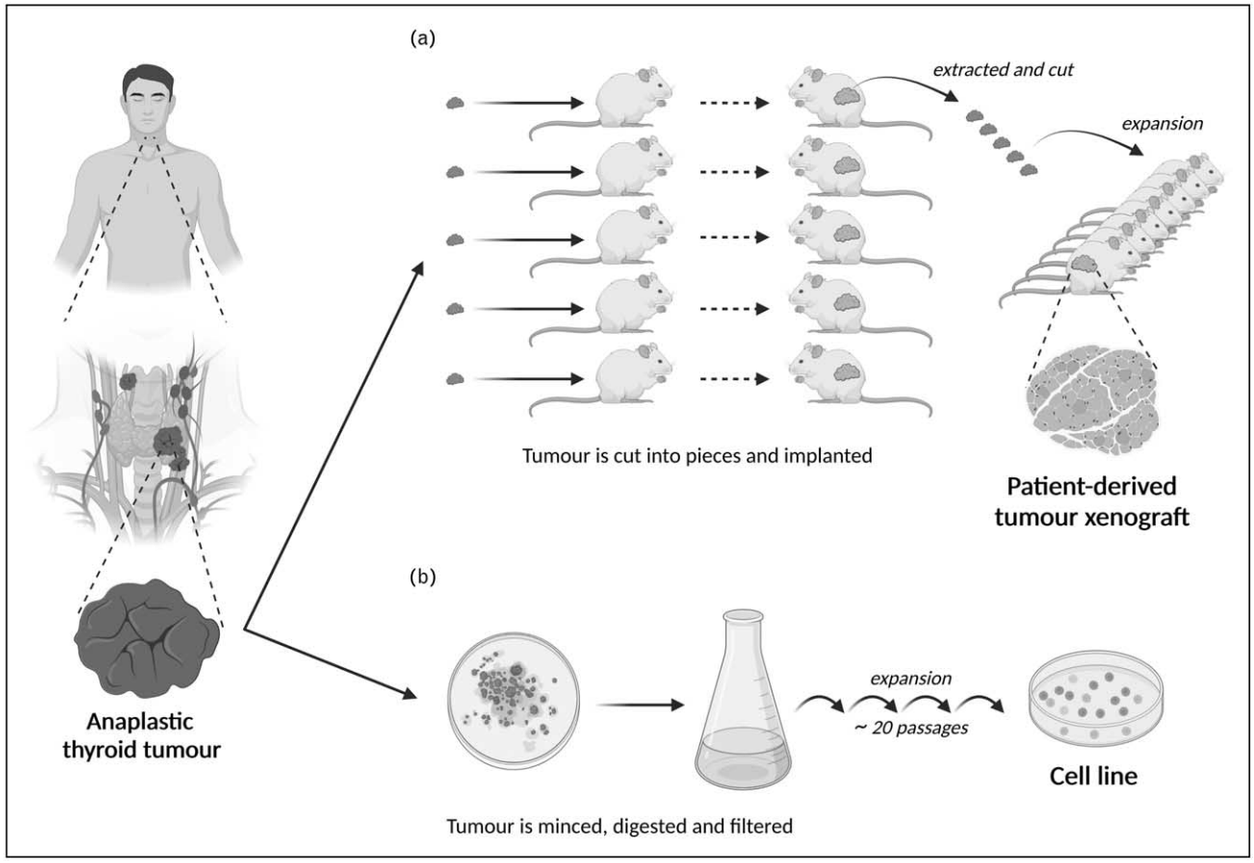

FIGURE 1. Schematic illustration of the main steps for obtaining cell lines or patient-derived tumour xenografts from a freshly resected primary anaplastic tumour. (a) To obtain patient-derived tumour xenografts (PDTX), tissues are firstly cut into small pieces and subcutaneously implanted into the flank of immune-compromised mice. After engraftment and growth of the tissue masses (which may take a few months), tumours are retrieved and sectioned. These are serially passaged into new mice generations for expansion, preparation of frozen tumour sections, and eventually evaluation of drug responses. Importantly, the resultant PDTX maintain the heterogeneity and the original tissue architecture of the primary tumour; (b) to derive a cell line, tissues have first to be finely chopped and incubated in a digestion solution (containing primarily collagenase and DNAse I). Obtained single tumour cells are then filtered and should be further purified/separated from remaining contaminating cells (red blood cells and stromal cells). Lines are usually considered established if immortalized cells are able to reach 20 passages. Generally, only the most outfitted tumour cell for in-vitro conditions is propagated. Image created with BioRender.com.

is still debatable. A Japanese single-arm phase II trial enrolling 51 patients, included 17 ATC [33]. These patients had an overall response rate (ORR) of 24%, a median progression-free survival (mPFS) of 7.4 months, and a median overall survival (mOS) of 10.6 months. Other retrospective studies reported some efficacy in ATC [34,35]. These findings lead to an international, multicentre, phase II trial, which was nevertheless stopped early because of futility (NCT02657369).

None of sorafenib, axitinib, gefitinib, or pazopanib have shown positive results. Unlike other thyroid cancers, tyrosine kinase inhibitors in monotherapy may have limited or no activity in ATC [36–39].

There is promising data with the combination of lenvatinib and pembrolizumab, an anti-PD-1 (programmed cell death 1) monoclonal antibody [40▪]. In this retrospective trial, six patients with metastatic ATC were treated, leading to 66% complete responses (CR) (4/6), 16% stable disease (SD) (1/6) and 16% progressive disease (PD) (1/6). mPFS was 16.5 months and mOS was 18.5 months. All patients with long-term (>2 years) or CR had either increased tumour mutational burden (TMB) or a PD-L1 TPS greater than 50%. Of note, the combination was toxic with grade III/IV toxicities requiring dose reduction/discontinuation of lenvatinib in approximately 50% patients. The interim results from the phase 2 ATLEP trial (NCT02973997) with the same

combination were presented during the 2021 Annual Meeting of the American Thyroid Association. The ORR after 3 months of treatment was 38.5% among the first 26 patients, which constituted all partial responses (PR). Additionally, 57.6% patients achieved stable disease. Only one patient had PD.

Targeted therapies

Patients with cancers harbouring a *BRAF V600E* mutation were treated in a phase II basket trial with the *BRAF* inhibitor dabrafenib 150 mg twice daily with the *MEK* inhibitor trametinib 2 mg once daily. This study also included 16 ATC patients and their ORR was 69% [41]. On the basis of this data, the combination received in 2018 FDA approval for the treatment of locally advanced or metastatic ATC with a *BRAF V600E* mutation and is now recommended in the most recently released guidelines as first-line therapy for those patients, if available [3▪▪,4,42–44]. This combination has also shown effectiveness in a neoadjuvant setting [45,46]. For all these reasons, the search of *BRAF V600E* mutation by a NGS is becoming a standard-of-care [4], and some groups have even proposed that immunohistochemistry (IHC) should initially be performed as more rapid diagnostic procedure, followed by expeditious confirmative molecular testing [3▪▪].

Among other potentially druggable genomic abnormalities are *ALK* translocations. If present, patients may benefit from treatment with *ALK* inhibitors such as crizotinib [47]. Additionally, everolimus, a mammalian target of rapamycin (*mTOR*) inhibitor, could be effective in case of *TSC2* mutations [48].

Larotrectinib and entrectinib are two FDA-approved *TRK* inhibitors for patients with solid tumours harbouring a *NTRK* fusion. Trials leading to its approval included thyroid cancer patients but detailed histological findings were not specified. All five subjects with thyroid cancers harbouring a *NTRK* fusion [49] achieved a response to larotectinib, PR in four cases and one CR. It is unknown if any of them had a diagnosis of ATC as detailed histology was not specified. Analogously to larotrectinib, entrectinib not only inhibits *TRK 1–3* but also the *ALK* and *ROS1* tyrosine kinases. Five patients with thyroid cancers whose pathology results were not detailed were enrolled in an entrectinib clinical trial and one patient achieved a PR [50]. In the presence of an *NTRK* fusion, commercial use of one of these two drugs, or inclusion in a clinical trial with an *NTRK* inhibitor can be considered [3▪▪].

Selpercatinib is an FDA-approved selective *RET* inhibitor for patients with either thyroid/lung cancer harbouring a *RET* fusion or *RET*-mutated medullary thyroid cancer (MTC). This approval was based on a phase 1/2 study including 170 patients with thyroid cancer, 19 of which presented *RET* fusion [51], and 2 of them had ATC. One of the two ATC patients responded for 18 months to selpercatinib. The use of selective *RET* inhibitors is recommended in the setting of clinical trials [3▪▪].

ALK fusions are very rare in ATC. Scarce data showing successful treatments with *ALK* inhibitors is available, on individual cases [47,52]. Similarly, it is recommended to treat these patients, if possible, in a clinical trial whenever possible [3▪▪].

Immunotherapy

Immunotherapy with antibodies targeting PD-1 receptor or PD-L1 has produced impressive results in many malignancies and completely changed the guidelines for tumours like melanoma and lung cancer, but few data are available on their use in ATC.

A subset of about 11–28% of ATCs express programmed death ligand-1 (PD-L1) in the tumour cells or the inflammatory environment, making those patients potential candidates for immunotherapies [53–56]. Immunoprofiling has also exposed high numbers of tumour-infiltrating lymphocytes in the tumour [57].

Spartalizumab, an anti-PD-1/PD-2 monoclonal antibody, was tested in pretreated patients with advanced ATC but assessments followed RECIST 1.1 response criteria [58]. The primary objective of the phase 2 part of the study was to determine the ORR, which was 19% (5 PR and 3 CR). The mOS was 5.9 months, with a 1-year survival of 40%, mPFS was 1.7 months. Interestingly, patients with less than 1% PD-L1 expression had a mOS of 1.6 months, and there were no responses in this group. Conversely, mOS was not reached in those with PD-L1 expression of 1–49% and at least 50%, and the ORRs were 18% (2/11) and 35% (6/17), respectively. For the 12 *BRAF V600E*-mutated ATC patients who participated in this trial, ORR was only 8%. Further data showing response to combination therapy with immunotherapy is anecdotal [59]. Retrospective data suggests improved outcomes when immunotherapy is added to targeted therapy in ATC [odds ratio (OR) 0.58; confidence interval (CI) 0.36–0.94], $P = 0.03$) [60].

A recent retrospective study [40▪] investigated the combination of pembrolizumab with lenvatinib in six ATC patients, reporting 66% CR and 16% SD, with a mPFS of 16.5 months. More details about this trial are mentioned earlier in this review.

According to guidelines [3▪▪], checkpoint inhibitors can be considered first-line therapy in the absence of other druggable abnormalities or as later line therapy, preferably in the context of a clinical trial, for patients with advanced disease and high PD-L1 expression. Nevertheless, immunotherapy is not FDA-approved, and it is often not available.

Mammalian target of rapamycin inhibitors

Everolimus is a rapamycin analogue that inhibits *mTOR*. Data from three trials enrolling patients with ATC with this drug are available [61–63]. Notably, all studies included less than 10 ATC patients, and none had more than one responder. However, two patients had an impressive response to everolimus. The trial by Hanna *et al.* [61], including molecular analysis of ATC tissue, reported one partial response in a patient who was progression-free until 17.9 months after study entry, and one had disease stability for 26 months. Despite the short mPFS in the ATC group, in the larger cohort of thyroid cancer, those with a mutation in the *PI3K*/*mTOR*/*AKT* pathway had a mPFS of 15.2 months and concluded that *PI3K*/*mTOR*/*Akt*-mutated ATC subgroups appeared to benefit from everolimus. One patient with ATC and a TSC2 mutation had a PR lasting nearly 18 months [48]. Another patient with an *NF1* mutation had stable disease lasting for 26 months. A larger trial with selected patients is needed to analyse to what extend patient selection for *PI3K*/*mTOR*/*AKT* pathway mutations could be important in ATC.

Vascular disrupting agents

Fosbretabulin is a prodrug of the investigational antimicrotubulin-disrupting agent combretastatin. This drug was studied in a phase 2 trial in ATC: no response was observed, but 7 out of 26 patients had a stable disease, with an OS of 4.7 months and a 1-year survival of 23% [64]. This molecule is currently not available on the market.

Ongoing trials

Combination of targeted therapy, immunotherapy, ChT and/or radiotherapy, administered together or sequentially in multidisciplinary ATC management regimens, may improve patient outcomes. Despite the rarity of this disease, several trials are ongoing, only some of them are mentioned.

One phase II trial combines atezolizumab with other molecules (bevacizumab, cobimetinib, nab-paclitaxel, paclitaxel and vemurafenib) for patients with anaplastic or poorly differentiated thyroid cancer (NCT03181100).

A combination of pembrolizumab with dabrafenib and trametinib before surgery for the treatment of *BRAF*-mutated anaplastic thyroid cancer is also currently studied (NCT04675710).

Another ongoing phase II trial studies abemaciclib (inhibitor of CDK4/6, which hinders *RB* activity) in metastatic or locally advanced anaplastic/undifferentiated thyroid cancer (NCT04552769).

A multitude of clinical trials with selective *NTRK* inhibitors are ongoing as basket trials including also ATC (e.g. NCT02576431, NCT02122913, NCT02568267, NCT02650401).

Several clinical trials using immunotherapy in combination with other systemic agents or with radiation are also underway (NCT03181100; NCT03122496; NCT02239900; NCT02404441).

CONCLUSION

Despite some improvement concerning the molecular profiling and the identification of potentially druggable targets, no cure is presently available for most ATC patients. Hopefully, further unravelling of the genetic alterations involved in ATC development and new preclinical models could define innovative approaches for individualized treatment for such patients.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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