

Evolution of anaplastic thyroid cancer management: perspectives in the era of precision oncology

Sarimar Agosto Salgado 

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Abstract: Anaplastic thyroid cancer is a rare aggressive malignancy resulting in poor outcomes, including significant morbidity and mortality. Historically, the overall survival of patients with anaplastic thyroid cancer has been less than 12 months. Multidisciplinary approaches combining surgery, radiation, and chemotherapy have been implemented to control this ominous disease. The evolution in science and technology has promoted deeper knowledge in the genetic pathways and mechanisms driving advance thyroid cancer. Furthermore, understanding molecular pathways resulted in the application of antineoplastic agents used in other tumors to thyroid cancer and the development of new highly selective drugs. A major landmark in anaplastic thyroid cancer management history was recently reached with the approval of BRAF and MEK inhibitor combination, specifically dabrafenib and trametinib for BRAF-mutated anaplastic thyroid cancer; this treatment has improved survival and outcomes in this population. Similarly, newer kinase inhibitors and immunotherapy are further shifting advanced thyroid cancer management to consider as first-line therapy inhibiting actionable oncogenic alterations. Therefore, newer treatment paradigms are incorporating molecular testing to provide personalized cancer care in anaplastic thyroid cancer. In this review, the principal aim is to provide an overview of the available international data on tyrosine kinase inhibitors and immunotherapy in the management of anaplastic thyroid cancer.

Keywords: anaplastic thyroid cancer, dabrafenib, precision oncology, trametinib, tyrosine kinase inhibitors

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Introduction

Thyroid cancer is the most common endocrine malignancy; in fact, the American Cancer Society anticipated for the United States 52,890 new thyroid cancer cases with 2,180 deaths for 2020.¹ Anaplastic thyroid cancer (ATC) is a rare cancer with the highest lethality of all thyroid malignancies.² Even though ATC accounts for only 1–2% of all thyroid cancers, this aggressive condition is responsible for 50% of thyroid cancer mortality.³ Although thyroid cancer trends have been studied during the recent years due to concerns of increase, the incidence rates of ATC have remained stable.^{4,5} Surveillance, Epidemiology,

and End Results (SEER) data analysis from 1986 to 2015 revealed an incidence of 0.9 cases per 1,000,000 of population; however, in non-whites and non-black races, incidence is up to 1.1 cases per 1,000,000 of population.⁵ Overall survival has been historically less than 1 year.^{3,6}

Commonly, ATC presents as one or more rapidly growing neck lesions, involving thyroid, neck nodes, and in certain circumstances infiltrating soft tissues, nerve structures, esophagus, and trachea.⁷ Therefore, evaluation for securing the airway is an essential step in assessing patients with suspected or biopsy-proven ATC.⁷ In addition,

Correspondence to:
Sarimar Agosto Salgado
Assistant Member,
Endocrine Oncologist,
Head & Neck-Endocrine
Oncology Department,
Moffitt Cancer Center,
12902 Magnolia Drive,
Tampa, FL, 33612 USA
[Sarimar.AgostoSalgado@
moffitt.org](mailto:Sarimar.AgostoSalgado@moffitt.org)

screening for distant disease, evaluation for feasibility of surgical resection followed by chemoradiation, and timely evaluation for BRAF mutation are critical steps in the managing these patients. The presence of distant metastases, tumor burden, and surgical eligibility have determined the subsequent phases of care.^{7,8} In addition, the patient's desires, comorbidities, and performance status play a role in determining treatment options. Involving palliative care early as collaborators in oncological care allows for additional assistance in symptoms management to maintain an optimal performance status within the clinical scenario. Goals of care discussions, assessment of the patient's support system, and advance directives are meaningful conversations that should occur early at diagnosis with periodical follow-up on patients' perceptions. Promoting communication is essential to ensure early identification of adverse events from any therapies.

Kitamura *et al.*² studied the cause of death of 106 cases of advanced thyroid cancer in Japan, including 37 cases of ATC; the most frequent lethal cause was respiratory insufficiency in 40.6% of the ATC cases, mostly due to pulmonary metastatic disease burden. Additional causes of death in ATC included circulatory failure (16.2%) due to major vessel obstruction, heart failure, or cardiac metastasis; airway obstruction (16.2%), tumor hemorrhage (13.5%), and other etiologies (13.5%) such as sepsis, renal insufficiency, disseminated intravascular coagulation, and hypercalcemia.² Given the lethality of ATC and limited responses to surgery, radiation, and cytotoxic chemotherapy, the field of oncologic endocrinology should strongly consider targeted therapies if the clinical scenario allows. As precision oncology field evolves with a deeper understanding of the driving forces of cell proliferation and cell survival, the options of targeting the specific main oncogenic alteration or driver mutation must be considered in ATC. Recently, Maniakas *et al.*⁹ retrospectively reviewed over 400 cases of ATC revealing significant increase in overall survival with the development of the era of targeted therapies; this study demonstrated a 24% increase in the 1-year overall survival (2000–2013 year cohort overall survival at 1 year was 35% *versus* 59% in the year group 2017–2019). In this review, the main objective is to highlight the evidence available on kinase inhibitors and immunotherapy in ATC.

Systemic therapies in ATC

BRAF^{V600E} mutated anaplastic thyroid carcinoma

BRAF^{V600E} mutation has been identified as the driver mutation in 45% of ATC cases.¹⁰ Preclinical data in BRAF^{V600E} mutant thyroid cancer cell lines and murine models revealed that BRAF inhibition resulted in diminished phosphorylation of ERK and MEK kinases in the mitogen-activated protein kinase (MAPK) signaling cascade (Figure 1).^{11–13} In addition, altered expression of genes regulating cell cycle transition, inhibition of cell proliferation, and migration affecting tumor aggressiveness have been demonstrated.^{11–13} Given the responses of BRAF mutant solid tumors (including melanoma and lung tumors) to BRAF inhibition and MEK inhibition, the use of BRAF inhibitors was studied in thyroid cancers including reports of utilization of this therapy in the redifferentiation of differentiated thyroid cancers and compassionate use of dabrafenib (a BRAF inhibitor) in patients with ATC.^{14–16} Falchook *et al.*^{17,18} presented the response data of dabrafenib monotherapy in the 14 patients with BRAF-mutated thyroid cancer who were enrolled in the phase I dose-escalation trial to evaluate this medication in melanoma, untreated brain metastases, and other solid tumors; in this thyroid cohort, there were 29% partial responses where nine cases had at least 10% tumor reduction by Response Evaluation Criteria in Solid Tumors (RECIST). Overall, for thyroid cancer cases, the median progression-free survival (PFS) was 11.3 months; one case with anaplastic histological features had a 66% decrease by RECIST, however classified as progressive disease response due to development of a new lesion.^{17,18} McFadden *et al.* highlighted with preclinical models the role of p53 function loss in the progression from differentiated thyroid carcinoma to ATC; furthermore, the implications that dual BRAF and MEK inhibition provided complete tumor regression and improved survival.¹⁹ Complementing the argument of targeting this pathway, a phase II randomized controlled trial comparing dabrafenib alone *versus* combination with trametinib (a MEK inhibitor) in BRAF mutant papillary thyroid carcinoma (PTC) cases revealed considerable preliminary objective response rates of 50% and 54%, respectively.²⁰ Of note, 25% of the 53 patients in this trial had up to three prior multikinase inhibitor lines of therapy.²⁰ As precision medicine evolves, the paradigms move to targeted

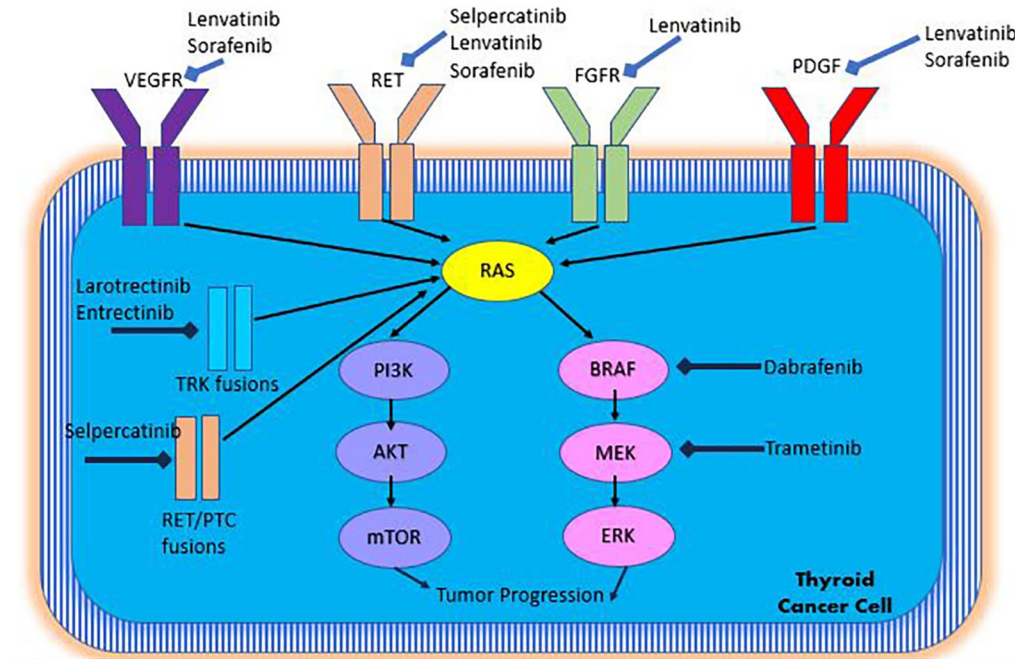


Figure 1. Schematic review of cellular pathways targeted by oral antineoplastic agents in thyroid cancer. Tyrosine kinase receptors including vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor α (PDGFR), and RET can activate internal MAPK pathways which can lead to tumor proliferation; in a similar way, TRK and RET fusions can lead to tumorigenesis. The figure above highlights several multikinase inhibitors described in this article with their respective target receptors or fusions. In addition, dabrafenib and trametinib inhibit BRAF and MEK, respectively, from the MAPK pathway which has led to improvement in survival on BRAF-altered ATC cases.

therapy as first line will continue to gain strength even in orphan diseases as ATC; nevertheless, it is still valuable to know for those cases treated initially with different systemic therapies that dual directed BRAF and MEK inhibition may still provide considerable responses. Subbiah *et al.*²¹ presented a compelling interim analysis of 16 patients with ATC on a phase II open-label trial combining dabrafenib and trametinib for BRAF-mutated tumors with an overall response rate (ORR) of 69% for the ATC cohort (including one complete response). The median age of enrolled ATC cases was 72 years (range, 56–85); majority were females and Eastern Cooperative Oncology Group performance status (ECOG) 1. In general, the toxicities in the ATC cohort were parallel to the experience of using these pharmacological agents in other tumors with fatigue being the dominant adverse event (44%). The most common adverse events for ATC cohort included fatigue, fever, nausea, vomiting, hyperglycemia, anemia, rash, and constipation with a frequency of 25% or higher (Table 1). Based on standard ‘Common Terminology Criteria for

Adverse Events’ (CTCAE), grade 3–4 events were anemia (13%), diarrhea, fatigue, and hyperglycemia with 6% each on the ATC patients on study.²¹ As a result, in 2018 the Food and Drug Administration (FDA) approved the combination of a BRAF inhibitor and MEK inhibitor, dabrafenib and trametinib, respectively, for treatment of BRAF-mutant ATC. Supporting data of experience outside the investigational framework has been reported, with 83% of patients experiencing clinical benefit, including scenarios where comorbidities or performance status would limit participation in clinical trials.²²

Targeted therapy and immunotherapy

Immune cells, specifically the T-cell family, express program cell death-receptor 1 (PD-1) on their surface, which interacts with a ligand on normal tissues; however, tumor cells express programmed cell death ligand 1 (PDL-1). The receptor–ligand interaction suppresses T-cell-mediated cytotoxicity toward the thyroid tumor.²⁹ The early response in tumor regression in

Table 1. Oral antineoplastic targeted therapies in thyroid cancer.

Systemic therapy	Molecular targets	Response rates	Common side effects
Dabrafenib and trametinib ²¹	BRAF and MEK	ORR 69% ^a	Fatigue, Fever, Nausea, Vomiting, Hyperglycemia, Anemia, Rash, and Constipation
Selpercatinib ²³	RET-altered tumors (including RET fusions)	Objective response 79% ^b 1-year PFS 64%	Dry mouth, Hypertension, Diarrhea, Constipation, Nausea, Edema, Elevated transaminases, QT prolongation
Larotrectinib ^{24,25}	NTRK fusions (TRKA, TRKB, and TRKC)	Objective response 79% 29% for ATC	Fatigue, Nausea, Vomiting, Diarrhea, Constipation, Dizziness, Cough, Anemia, Fever
Entrectinib ²⁶	TRKA, TRKB, and TRKC, ROS-1, and ALK	50% PR 7% CR ^c	Dysgeusia, Constipation, Fatigue, Edema, Dizziness, Paresthesia, Nausea
Lenvatinib ²⁷	FGFR, VEGFR, KIT, RET, PDGF α (multikinase inhibitor)	PFS 18.3 months ²⁷ 64.8% Response Rate in RAIR-DTC 63% PR in RAIR-DTC ²⁷ Objective response rate 24% in ATC ²⁸ PFS 7.4 months in ATC	Hypertension, Anorexia, Fatigue, Gastrointestinal disturbances, Proteinuria

ALK, anaplastic lymphoma kinase; ATC, anaplastic thyroid cancer; CR, complete response; FGFR, fibroblast growth factor receptor; NTRK, neurotrophic-tropomyosin receptor kinase; ORR, overall response rate; PDGF α , platelet derived growth factor; PFS, progression-free survival; PR, partial response; RAIR-DTC, radioactive iodine refractory differentiated thyroid cancer; RET, rearranged during transfection; ROS1, c-ros Oncogene 1 kinase; VEGFR, vascular endothelial growth factor receptor.

^aOverall response rate (ORR) in ATC cohort.

^bIn RET-altered thyroid cancer cohort ($n=19$) including two ATC cases.

^cResponses by RECIST 1.1 for NTRK-positive tumors (10 different tumor types—19 histologies).

BRAF-mutated ATC after combination of BRAF/MEK inhibition has led way of incorporating this therapy after rapid detection of a BRAF mutation in a neoadjuvant approach.²¹ A great example is the dramatic response to dabrafenib administered via gastrostomy in a BRAF^{V600E} and p53 mutated unresectable ATC.³⁰ In this case, the tumor exhibited locally aggressive behavior given invasion to pharynx, esophagus, paraspinal muscles with extensive cervical lymphadenopathy, and mediastinal extension; however, dabrafenib therapy allowed the patient to resume oral intake with significant improvement in compressive symptoms within 2 days of initiation of therapy.³⁰ Trametinib was added subsequently and 1-month post-systemic therapy initiation, progression was noted on a supraclavicular lymph node. The proposed culprit of progression was the development

of a new RAS mutation, which has been a reported mechanism of resistance after blockade of the MAPK pathway with BRAF and MEK inhibitors.^{30–32} Immunohistochemistry revealed elevated program death ligand (PDL-1) score which has been potentially associated with responses to immunotherapy. Pembrolizumab was therefore added to his systemic therapy regimen, which permitted eventual total thyroidectomy, bilateral central and lateral neck dissection followed by post-surgical chemoradiation, and resumption of systemic therapy. This resulted in durable response 16 months after diagnosis.³⁰ Based on the same management principles illustrated in the prior example, a six-patient case series of neoadjuvant use of dabrafenib plus trametinib (DT) for BRAF^{V600E}-altered ATC promoted a complete resection achieving locoregional control with

overall survival at 1 year of 83%.³³ Remarkably, most patients in this series who were treated with pembrolizumab plus DT were disease-free at approximately 20-month follow-up.³³

There are multiple case reports of immunotherapy, specifically PD-1 receptor blockers such as nivolumab or pembrolizumab, as therapeutic modalities for ATC in combination with kinase inhibitors with favorable responses.^{34,35} These data are sustained by preclinical murine models.^{34,35} Undifferentiated carcinoma has higher rates of PDL-1 expression when compared with differentiated thyroid cancer with reported ranges from 20% to 90% of ATC.^{29,36} The incorporation of the PD-1/PDL-1 axis into the models for the care of management advanced de-differentiated thyroid cancers should be further explored given the encouraging experience with BRAF inhibitors. The specific response data from the ATC cohort of a phase II international basket trial for spartalizumab was recently examined in 42 thyroid cancer cases between the ages of 46 and 83 (median, 62.5 years).³⁷ In summary, overall the cohort had good performance status (ECOG 1=25; 59.5%) where more than half of the patients were males and 30 cases (71.4%) had prior history of radiation therapy.³⁷ Twenty-five patients (60%) had one or more systemic therapies in their oncologic history which is not surprising given majority of the cohort had lung metastases ($n=35$; 83%).³⁷ Central pathology review in 40 cases corroborated ATC histology in 90%; ORR by RECIST to this PD-1 targeting monoclonal antibody was 19%.³⁷ Of note, an interesting fact of this study is the effect on PFS and overall survival when the cohort is stratified by percentage of PDL-1 expression. Specifically, the remarkable contrast between cases with PDL-1 expression <1% versus PDL-1 $\geq 50\%$ in which 1-year PFS was at 0% and 29%, respectively.³⁷

Median overall survival (OS) was 1.6 months in those with negative PDL-1 score which diverged with the OS not reached at time of data cut on high PDL-1 cohort. Overall, spartalizumab 400 mg IV every 4 weeks had a tolerability similar to alternative immunotherapy regimens with dominant adverse events including diarrhea (11.9%), pruritus (11.9%), fatigue (7.1%), and pyrexia (7.1%).³⁷ In addition, case series of patients with ATC treated on kinase inhibitors including dabrafenib/trametinib or multikinase

inhibitors such as lenvatinib have received immunotherapy at the time of progression with clinical benefit documented in 9 out of 12 patients (75%); this included five partial responses and four stable disease cases.³⁸ The median overall survival post-pembrolizumab addition to kinase inhibitor was 6.9 months.³⁸

Further study of the role of immunotherapy in ATC, specifically atezolizumab combined with kinase inhibitors, has been investigated in a prospective single-center clinical trial stratifying the treatments based on the driver mutation.³⁹ BRAF-mutated ATC received vemurafenib/cobimetinib (BRAF/MEK inhibitor) combined with atezolizumab; RAS and NF1/2 mutated ATC patients received cobimetinib plus atezolizumab and if none of the prior mentioned mutations noted, patients would receive bevacizumab plus atezolizumab if no contraindications for a total of 34 patients in these 3 groups. The overall survival of the three cohorts combined was 18.2 months.³⁹ This preliminary data shows promise of upfront combination of kinase inhibitor therapy with immunotherapy tailored to specific driver mutations in ATC.

Additional targeted therapies and multikinase inhibitors in ATC

Rearranged during transfection (*RET*) protooncogene fusions are rare driver alterations in ATC as demonstrated by multiple studies evaluating molecular profiling; this mutation occurs overall approximately in less than 10% of differentiated thyroid cancers.^{10,40–42} Recently, a high selective *RET* inhibitor, selpercatinib, was approved in the United States after the positive findings of the phase 1–2 trial on *RET*-mutated advanced medullary thyroid carcinoma and *RET*-altered advanced metastatic thyroid cancer (Figure 1).²³ Specifically, among the 19 cases of *RET* fusion positive advanced thyroid cancer, there were two patients of ATC (11%) and three poorly differentiated thyroid cancers (16%).²³ The median age of patients in this cohort was 54 years with a median amount of four prior therapeutic regimens (range, 1–7); six patients had brain metastases (32%). In this cohort, objective response was 79%. Of note, there is evidence of central nervous system penetration of this medication facilitating the treatment of brain metastatic disease in patients with advanced thyroid cancer.^{43,44} In terms of the side-effect profile of this medication, the highest

frequency of low-grade adverse events were due to gastrointestinal complaints, elevated transaminases, and dry mouth (Table 1).²³ More severe grade 3–4 events included hypertension (21%) and elevated liver enzymes (11% alanine aminotransferase and 9% aspartate aminotransferase).²³ In the findings of the completed trial for RET-altered tumors (cohort of more than 500 RET-positive solid tumors), only 2% of patients discontinued selpercatinib due to medication-related complications.²³

Another example highlighting the positive effects of comprehensive molecular testing is the option of larotrectinib for *NTRK* fusions (Figure 1). Neurotrophic-tropomyosin receptor kinase (*NTRK*) fusions have been reported in less than 3% of thyroid cancers as the driver alteration for tumorigenesis.^{45,46} The potential targetability of this fusion by specific antineoplastic agent as larotrectinib has studied in research protocols including a variety of *NTRK*-fusion positive tumors including sarcomas, lung, thyroid, salivary tumors, breast, gastrointestinal, hepatic, and pancreatic carcinomas with overall partial responses reported in 63% (97 of 159 patients).²⁴ In the data from a pooled analysis of several trials, 24 thyroid patients were evaluated with responses in 79% (19 cases); a limitation is the lack of specific details of histopathological variants.²⁴ The majority of adverse events related to larotrectinib are grade 1–2 including fatigue, gastrointestinal disturbances (including nausea, vomiting, diarrhea, or constipation), dizziness, cough, anemia, and fever. Supporting the safety of this tropomyosin receptor kinase (TRKA, TRKB, and TRKC), selective inhibitor is the fact that higher severity grade events (grade 3–4) occurred in lower frequencies, for example, alanine aminotransferase elevation (3% grade 3 and <1% grade 4), neutropenia (2% grade 3 and <1% grade 4), and grade 3 anemia (2%).²⁴ A subset analysis by Cabanillas *et al.*²⁵ on thyroid cancer cases revealed ORR 75%, specifically 29% for ATC. Another therapeutic alternative for *NTRK* fusion positive thyroid tumors is entrectinib, which is an inhibitor of TRKA, TRKB, and TRKC, ROS-1 and ALK altered tumors with overall 50% partial responses.²⁶ In the pooled analysis, there were five patients with thyroid cancer with one patient included in the response analysis.²⁶ Higher severity side effects included nervous system disorders (<5%); nevertheless, the general majority of

adverse events were grade 1–2.²⁶ Although there is lack of specific data on the ATC population on both these medications, given the rarity and lethality of ATC, it is essential to perform molecular testing including fusion testing to evaluate for potential treatment with selective inhibition.

In the United States, there are several approved oral chemotherapeutic agents denominated as multikinase inhibitors for radioactive iodine refractory differentiated thyroid cancer (RAIR-DTC). Lenvatinib targets several kinase receptors, including fibroblast growth factor receptors (FGFR), vascular endothelial growth factor receptors (VEGFR), KIT, RET, and platelet derived growth factor α (PDGF α); of note, several of these receptors are present both on thyroid cancer cells and peritumoral blood vessels, accounting for the antiangiogenic potential of this medication (Figure 1).²⁷ The median PFS of RAIR-DTC cases treated with lenvatinib compared with placebo was 18.3 months *versus* 3.6 months, respectively, in a multicenter double-blinded randomized trial.²⁷ This led to approval of this antineoplastic regimen for RAIR-DTC. In addition, there was evidence of overall survival benefit in the RAIR-DTC population above 65 years of age.⁴⁷ Multiple studies in Japan have explored the specific responses of lenvatinib in ATC, revealing expected toxicity profiles based on the drug mechanism of action such as hypertension, anorexia, fatigue, gastrointestinal disturbances, and palmar-plantar erythrodysesthesia (hand-foot syndrome).^{28,48} In terms of efficacy, in a cohort of 17 patients with ATC, 71% had stable disease ($n=12$) and 24% partial response ($n=4$) with median PFS 7.4 months.²⁸ Retrospective data has also noted responses in unresectable ATC.⁴⁹ Sorafenib has similar multikinase targets as lenvatinib with the addition of certain RAF inhibition; this medication has proven median PFS 10.8 months *versus* 5.8 months in RAIR-DTC.⁵⁰ Data from Japanese groups in Sorafenib-treated patients with ATC reveal median PFS less than 3 months and overall survival 5 months.⁵¹ Therefore, responses in ATC are less durable when compared with data noted for RAIR-DTC. As timely implementation of next generation sequencing and liquid biopsy methods increases in availability and accessibility, the paradigms in treating advanced thyroid cancer (including ATC) will continue shifting toward inhibiting a targetable mutation.

Conclusion

In recent years, the progress in technology, genetic sequencing, and drug development has allowed for significant improvements in the care of patients with advanced thyroid cancer, particularly ATC. Specifically, the dramatic responses in BRAF-mutated ATC and feasibility of less morbid surgical interventions in cases amenable for neoadjuvant approaches have offered better outcomes including improved survival to a population with a highly lethal disease. In addition, combinations of immunotherapy and kinase inhibitors may pose a reasonable alternative for certain ATC cases. Although the data reviewed above demonstrate potential responses upon targeting specific fusions as well as detailing some of the experience with multikinase inhibitors, there is still limited information to provide strong recommendations for some of these therapeutic approaches outside the structure of a clinical trial. Therefore, it is crucial to (a) attempt enrollment in research protocols if possible and (b) if no available trial options, a transparent discussion with patients regarding the latest available evidence in medical and layman terms prior any off-label use of medications. As ATC consist of rapid progressive tumors, many cases warrant a bridging cytotoxic chemotherapy dose while awaiting immunohistochemistry, liquid biopsy, and molecular tumor testing. Multidisciplinary care is essential for determining the best individualized approach to every patient with ATC maximizing efficacy, tolerability, and quality of life. Incorporating molecular testing is key to a personalized approach given the potential to detect an actionable oncogenic alteration, resulting in expanding treatment routes.

Author contributions

SAS-Conceptualization, Investigation, Writing Original Draft, review and editing


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ORCID iD

Sarimar Agosto Salgado  <https://orcid.org/0000-0001-5630-0609>

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