# Anaplastic Thyroid Cancer

## New Horizons and Challenges

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**KEYWORDS**

• Anaplastic thyroid cancer • Targeted therapy • BRAF/MEK inhibitor • Surgery • Multidisciplinary • Immunotherapy • Clinical trial

**KEY POINTS**

- Anaplastic thyroid cancer (ATC) remains a highly aggressive and deadly disease, requiring rapid referral to a highly specialized center
- *BRAF* mutation status must be obtained rapidly to determine BRAF/MEK inhibitor eligibility
- Enrollment in clinical trials may offer the best chance for survival and overall quality of life to a patient with ATC
- With the advent of novel therapeutics and rapid/favorable response to systemic therapy, patients with initial locoregional and/or metastatic disease may become eligible for surgery

### BACKGROUND

Historically, anaplastic thyroid cancer (ATC) has been considered one of the most aggressive and lethal malignancies, which presents itself at a median age of 65 to 70 years,[1,2] with median overall survival (OS) of 4 months and a 6-month OS of 35%,[1] whereas disease-specific mortality approaches 100%.[3,4] Therefore, although ATC comprises 1% to 1.5% of all thyroid cancers, it represents more than half of the annual thyroid cancer-related mortality[5] because of its deadly and rapidly progressing nature. It is primarily due to this aggressiveness that the American Joint Committee on Cancer has classified all ATC as stage IV.[6]

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Part of the challenge of understanding and treating ATC is that its tumorigenesis remains unclear. At present, the 2 main theories are that ATC arises either following the dedifferentiation of differentiated thyroid cancer (DTC) and poorly differentiated thyroid cancer (PDTC) or de novo[7] and the following are associated risk factors: a long-standing goiter, history of prior radiation, and history of prior treated DTC or PDTC with a rapidly evolving recurrence. Recent evidence on the coexistence of BRAF-mutated ATC with PTC suggests a potential likely common PTC origin for most of these tumors.[8–10] Although thyroid cancer, in general, is not considered a malignancy with a high tumor mutational burden (TMB), it has been shown that ATC has a higher relative mutational burden,[7] although TMB is low when compared when other solid tumors. Accumulation of genetic variations for ATC tend to occur in tumor suppressor genes (*p53*, *PTEN*), oncogenes (*TERT* promoter, *RAS*, *BRAF*, *PIK3CA*), oncofusions (*NTRK*, *RET*, *ALK*), or through mismatch repairs (**Fig. 1**).

Traditionally, ATC treatment provided minimal survival benefit, often being disease palliation oriented and seldom curative. Surgery alone is rarely beneficial, because patients' locoregional and metastatic tumor burden is often a significant factor at presentation, rendering them inoperable. Conventional cytotoxic chemotherapy has been shown to provide little to no benefit, even when combined with external beam radiation therapy, while causing significant side effects. Fortunately, recent advances in ATC treatment have shown remarkable shifts in outcomes and OS rates in the last decade,[2] which have also prompted the scientific community to update the American Thyroid Association Guidelines for ATC[11] for the first time in a decade to better transmit these changes and options for patients.

## EXPERT MULTIDISCIPLINARY MANAGEMENT AND ACCESS TO CLINICAL TRIALS

Considering the rapidly evolving nature of ATC and its slight increased incidence in the United States in the past few decades,[12] it is important that physicians identify these cases in a timely fashion to ensure prompt clinical, radiologic, and molecular workup. With current median survival rates estimated at 9 months,[2] any delays in diagnosis and disease extent evaluation can be detrimental for patients and their OS. Having access to highly specialized multidisciplinary teams in cancer centers allows patients to receive thorough tumor workups, including rapid immunohistochemistry and cell-free DNA analyses,[13] while giving them access to select clinical trials specific to ATC, seldom found in most community and even tertiary centers. One such highly specialized program was developed in 2014 at the University of Texas MD Anderson Cancer Center, where patients are fast-tracked for multidisciplinary evaluation along with imaging and tumor molecular testing within 7 days. This Facilitating Anaplastic Thyroid Cancer Specialized Treatment (FAST) team[14] has increased clinical trial participation for patients with ATC 4-fold in less than 5 years,[2] allowing for ATC-specific trials to rapidly reach accrual and timely completions. Such trials[15] led to the US Food and Drug Administration (FDA) approval of dabrafenib with trametinib in May 2018 for patients with *BRAF*V600E-variant ATC, representing the first drug therapy approved by the FDA for ATC. Since then, several clinical trials are underway or have been completed, and are further discussed in this review.

Overall, what remains evident is that when dealing with such an advanced and deadly disease, physicians should always strive to treat patients on protocol, as much as possible, because this will not only ensure patients receive the most promising therapeutics but also allow us to learn as much as we can on disease evolution and its response to treatment. Through patient biopsies and/or surgical specimens, we are able to collect the highest level of clinical data possible, allowing us to further

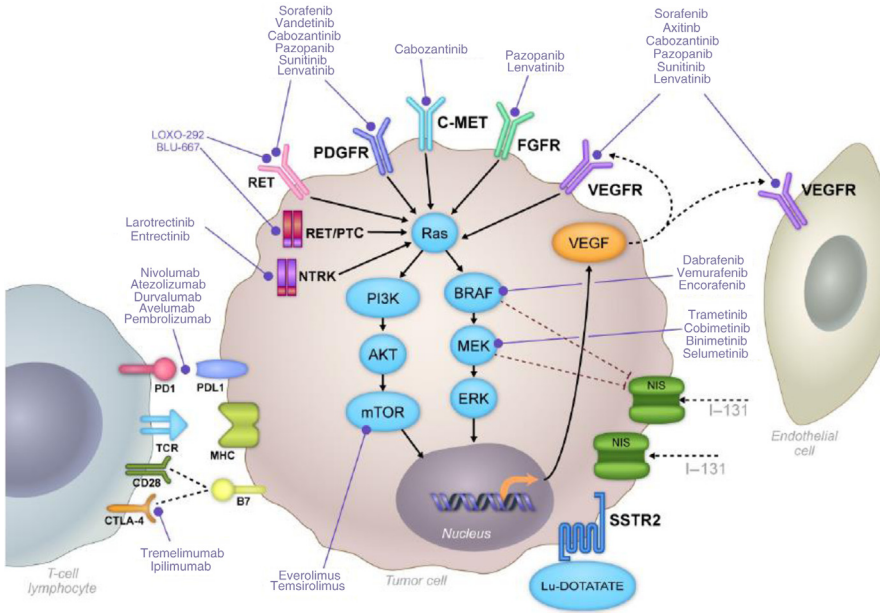


**Fig. 1.** Anaplastic thyroid cancer therapy according to pathway targeted. (*From* Cabanillas ME, Ryder M, Jimenez C. Targeted Therapy for Advanced Thyroid Cancer: Kinase Inhibitors and Beyond. Endocr Rev. 2019 Dec 1;40(6):1573–1604; with permission.)

study the disease and develop preclinical models for translational research and novel therapeutics development.[16,17]

## MODERN THERAPIES FOR ANAPLASTIC THYROID CANCER

Initial treatment decisions for ATC start with determining resectability of the primary tumor. Although rare (10%[2]), patients with stage IVA (confined to the thyroid gland) disease should undergo upfront surgery followed by chemoradiation. Owing to the recognition that patients with *BRAF*V600E-mutated ATC respond favorably to BRAF-directed therapy, identification of those with a *BRAF*V600E mutation is now the pivotal decision point when determining initial treatment in patients with stage IVB (extends outside the thyroid gland and/or metastatic to regional lymph nodes) and IVC (distant metastatic disease) disease. Patients with stage IVB disease who are resectable can either undergo upfront surgery or, in select cases, neoadjuvant targeted therapy treatment before surgery. These patients should then undergo chemoradiation. Patients with stage IVC disease (>50%[2]) are the most difficult to treat. *BRAF*V600E-mutated patients should be initiated on BRAF-directed therapy. Non-*BRAF*V600E-mutated patients should, preferably, be offered a clinical trial when available, immunotherapy-based treatment if programmed death-ligand 1 (PD-L1) score is high, or supportive care/hospice.

### *Testing for BRAFV600E Mutation*

Rapid identification of a *BRAF*V600E mutation must be a priority. Immunohistochemistry (IHC) staining for *BRAF*V600E, which tests for protein expression, may yield results in 24 to 72 hours, depending on the availability of the antibody. Of note,

multiple biopsies, preferably core biopsies, should be performed because ATC tumors often present with large, nonviable, highly necrotic tissue, which may be difficult to adequately sample. Tissue-based next-generation sequencing (NGS) is, however, the gold standard for determination of BRAF status, although NGS through circulating cell-free DNA (cfDNA) liquid biopsy is also useful for results in approximately 1 week.[18] The latter has gained significant grounds in cancer genotyping because it offers a minimally invasive and reliable method to gain real-time tumor molecular profiling.[19] The use of cfDNA in ATC was first described in 2017 by Sandulache and colleagues[20] where the Guardant360 platform was used and had a 100% concordance rate for the *BRAF*V600E mutation between blood-drawn liquid biopsy and tumor molecular testing in untreated patients. A follow-up study showed 93% concordance between these.[18] This tool has since been used to not only evaluate the molecular profiling of patients with ATC at presentation and help guide treatment selection but has also recently been shown to aid in evaluating patient prognosis.[18]

### *BRAFV600E-Mutated Anaplastic Thyroid Cancer*

The most significant targeted therapy to truly shift the pendulum for ATC management was the combinatorial use of BRAF/MEK inhibitors in patients harboring a *BRAF*V600E mutation.[15] Once a *BRAF*-mutated ATC has been identified, BRAF-directed therapy or chemoradiation therapy should be started in patients presenting with tumor burdens that are not amenable to upfront complete surgical resection. When successful, BRAF-directed therapy has been shown to induce rapid and significant tumor regression, potentially rendering patients, who were previously inoperable as, candidates for surgery. In the first such report, Wang and colleagues[8] demonstrated the remarkable tumor response to dabrafenib + trametinib in 6 patients who then underwent standard surgical resection of their thyroids and neck disease, even though they were either inoperable at presentation or would have required morbid surgeries involving the laryngopharyngoesophageal complex. The ability to offer complete locoregional surgical resections has been associated with some of the highest survival rates ever reported for advanced ATC to date, with a 94% 1-year survival and an unmet median OS in a cohort of 20 patients (8 of 20 having stage IVC disease) having received BRAF-directed therapy followed by surgery.[2] These findings have prompted the conception of a multicenter phase 2 clinical trial (NCT04675710) that will study the effect of dabrafenib + trametinib in combination with pembrolizumab before surgery, with the primary aim to attain complete gross surgical resection (R0: clear, or R1: microscopically positive surgical margins).[21]

### *Resistance to BRAF-Directed Therapy*

Unfortunately, as reported with melanoma[22] and non–small cell lung cancer,[23] patients on BRAF/MEK inhibitors will invariably develop resistance that is frequently caused by the upregulation of growth factor receptors, the use of alternative pathways, or the reactivation of the mitogen-activated protein kinase and/or the PI3K/AKT pathways, which were initially inhibited.[24–26] More recently, de novo *RAS* mutations in *BRAF*-mutated thyroid cancer have been reported in an in vitro setting[27] following long-term vemurafenib exposure, whereas case reports have also been published in which patients with *BRAF*V600E-mutated thyroid cancers previously on BRAF/MEK inhibitors developed de novo *RAS* mutations in conjunction with disease progression.[28,29] Thus, what was previously believed to be a mutually exclusive path to tumorigenesis,[30] there is clear evidence that *RAS* mutations can occur in this population, and accurately identifying them may allow physicians to offer further

therapeutic options with the advent of 2 new molecules being actively studied for *RAS*-mutated cancers.[31,32] Immunotherapy, in conjunction with the BRAF/MEK inhibitor therapy has also gained significant interest in the quest for inhibiting resistance, with reported results showing favorable outcomes.[33,34]

### *Immunotherapy for Anaplastic Thyroid Cancer*

Despite the initial favorable antitumoral effect of combination therapy, patients will often develop resistance to therapy, whether it be through upregulation of growth factor receptors, development and/or use of alternative pathways, or mutation of proteins in signaling cascades. Therefore, combination therapy not only helps combat the disease but also helps combat treatment resistance development. Furthermore, because the *BRAF*V600E mutation is only found in approximately 30% to 40% of ATC tumors,[2,35] a significant proportion of patients will be ineligible to receive dabrafenib + trametinib, and other effective systemic agents are needed for the locoregional advanced and/or metastatic disease.

Human ATC tissue analyses have shown that there is a high PD-L1 expression and high frequency of tumor-infiltrating lymphocytes, suggesting an active immunogenic environment that may be targetable with immunotherapy.[36,37] To date, the use of immunotherapy in a monotherapy setting for ATC has shown modest results, with spartalizumab offering a 19% overall response rate[38] in a mixed *BRAF*-mutated and nonmutated cohort. Patients with tumors having higher PD-L1 scores had more favorable response rates and OS. Lower-than-expected responses in this trial may have been associated with the low PD-L1 expression scores seen on IHC in several of the patients enrolled in the trial (as low as <1%).

In contrast to monotherapy, combining targeted therapy with immunotherapy has shown great promise, both in in vivo preclinical trials in which anti PD-L1 therapy was shown to potentiate the effect of BRAF-directed therapy[39] and in the clinical setting with multiple retrospective reports.[2,33,40–42] Another checkpoint receptor, cytotoxic T lymphocyte antigen 4, is also being targeted in patients with ATC with a checkpoint inhibitor, ipilimumab, in a trial involving the combination of nivolumab (PD-L1 inhibitor) and ipilimumab. Ten patients with ATC received the combination, of which 30% had profound partial responses and 2 remain without any evidence of disease after 13 and 26 months of follow-up.[43]

Upfront use of lenvatinib in combination with checkpoint inhibitors can offer an adequate tumor response, as seen in the in vivo preclinical murine model by Gunda and colleagues.[44] Retrospective data on this combination showed extremely favorable responses, although the cohorts remained small (4 of 6 complete remission, 1 of 6 stable disease, and 1 of 6 disease progression).[45] This prompted the same investigators to commence a prospective phase 2 trial (ATLEP trial), evaluating the efficacy and safety of this combination treatment, with the primary end point being reached thanks to a best overall response of 37.5% for patients with ATC.[46] Recently, the investigators presented their interim results from this trial with an ATC-specific overall response rate of 68% and a clinical benefit rate of 100%. However, the elevated rate (53%) of severe (grade III/IV) adverse events, such as fistula development (11%), arterial hemorrhage (11%), and aspergillus pneumonia (11%), among others, should be noted and followed closely as the trial nears completion.[47]

At present, several prospective clinical trials are underway to evaluate the individual and synergistic effect of targeted therapies and checkpoint inhibitors, including one of the largest that is enrolling BRAF-mutated, RAS-mutated, and non-BRAF/non-RAS-mutated patients to try and capture as large an ATC population as possible.[34]

### *Other Therapies*

Apart from immunotherapy and BRAF-directed therapies, other targetable genetic variations have been identified in ATC, for which the FDA has recently granted drug approvals. Although seldom found in ATC, these include the *NTRK*[48,49] (2%–4% of ATCs), *ALK*[50] (4% of ATCs), and *RET* fusions[51] (1% of ATCs). Specifically for the NTRK-directed therapy using larotrectinib, 7 patients with ATC have received it, of which 2 had a partial response (29%), whereas 1 had stable disease, 1 could not be determined, and 3 progressed.[52] Although the response was notable in 2 of 7, the effect was short lived because disease progressed within a few months.[53] Recent findings demonstrated that short-lived *RET* fusion-positive thyroid cancers have been treated with selpercatinib[54] or pralsetinib,[55] showing encouraging tumor response rates, although the number of ATC cases treated have been limited to allow for robust conclusions for the time being. In general, these drugs should be used in the setting of a clinical trial when possible.

Pazopanib, a tyrosine kinase inhibitor, was evaluated in a multicenter randomized placebo-controlled phase 2 trial of concurrent intensity-modulated radiation therapy (IMRT) and paclitaxel, as prior preclinical in vivo data had shown a potential synergistic mechanism.[56] Although the randomized trial reported no increase in adverse events, there was also no difference in OS (1, 2, and 3-year) when adding pazopanib to IMRT + paclitaxel.[57] Of note, both the placebo and pazopanib cohorts had significantly lower OS rates than those reported in studies using BRAF/MEK inhibitors with or without checkpoint inhibitors, further strengthening the argument that classic cytotoxic chemotherapy with IMRT should not be the initial treatment of patients with ATC, with or without a tyrosine kinase inhibitor.

Following a favorable response in a small-scale phase 2 trial conducted in Japan evaluating the efficacy of the multikinase inhibitor lenvatinib in patients with ATC (24% partial response rate),[58] a larger-scale, single-arm multicenter phase 2 trial[59] was conducted to further evaluate the role of this drug for ATC. Although the safety profile of lenvatinib was acceptable, the interim analysis overall response rate was 0%, halting the study altogether, with one patient ultimately achieving partial response (overall response rate of 2.9%).[59] Similar findings have been reported with other multikinase inhibitors used in monotherapy settings for ATC, such as sorafenib[60] and pazopanib,[61] with little to no tumor response observed. Given these results, monotherapy with multikinase inhibitor therapy is not recommended.

## GOALS OF CARE CONVERSATION

With several treatment options continuously emerging, the future of ATC care is promising. However, even in the most specialized cancer centers, median OS has only reached 16 months for this disease.[2] The reality remains that ATC has a high mortality rate, often due to its advanced disease presentation with rapid growth and treatment resistance. Having a "goals of care" discussion at an early stage and early involvement of supportive care physicians are therefore important. These conversations include understanding and identifying advanced directives, code status, and surrogate decision makers, while candid discussions where patients understand the prognosis, treatment goals, and side effects of treatment are equally critical. Overall, although prognosis for ATC has improved, most patients with an ATC diagnosis will endure a long (often life-long) treatment course and ultimately still succumb to their disease. Therefore, patients' and their families'/caregivers' expectations must be managed at the outset, with an appropriate awareness of palliative care and hospice care options, should they become necessary.

## ACCESS AND COST OF CARE

It is of utmost importance that patients with ATC be managed in highly specialized centers with rapid evaluation and treatment protocols specific to patients with ATC. Physicians in peripheral and/or low-volume ATC centers should establish an efficient rapid-referral process from their respective centers to centers with ATC care expertise to avoid treatment delays. As most novel therapeutics are expensive, patient financial toxicity must also be considered, with clinical trials offering opportunities for some patients to receive drugs. Finally, many targeted therapies have limited to no availability worldwide, or are cost prohibitive, limiting the scope to which novel treatment paradigms can be applied globally.

## SUMMARY

ATC is a challenging malignancy to treat on account of advanced presentation, short window of opportunity from diagnosis to treatment commencement, and high rate of treatment resistance. As molecular drivers for tumorigenesis continue to be elucidated for ATC and other aggressive human malignancies, new drugs and drug combinations will hopefully continue to offer life-extending benefit by overcoming treatment resistance. For many patients, ATC treatment has now shifted from a palliative to curative approach, with the goal to offer patients significantly longer survival and quality of life. Ongoing and future studies will continue to refine the role of novel targeted therapies and immunotherapy in ATC management.

## CLINICS CARE POINTS

- Patients with ATC often present with rapidly growing neck masses that may involve vital structures such as the trachea and recurrent laryngeal nerve, rendering the patient at risk for airway obstruction and/or aspiration. Evaluation by a head and neck surgeon, with securing of the airway, if necessary, should be performed before any other workup.
- Identification of *BRAF* mutation status should be prioritized in the initial workup of all patients presenting with a rapidly growing thyroid mass. Immunohistochemistry provides the quickest yield and should be preferentially performed on tissue-based biopsies, with additional specimens sent for NGS. PD-L1 percent analyses should also be conducted to evaluate tumor immunogenicity and potential response to checkpoint inhibitors.
- Stage IVA ATC should be managed with upfront surgery followed by chemoradiation. Stage IVB tumors that are resectable should be treated with upfront surgery or, in select cases, neoadjuvant targeted therapy treatment before surgery, followed by chemoradiation. Stage IVC *BRAF*V600E-mutated tumors should be treated with BRAF-directed therapy, whereas non-*BRAF*V600E-mutated tumors should, preferably, be offered a clinical trial when available, immunotherapy-based treatment if PD-L1 score is high, or supportive care/hospice.

## DECLARATION OF INTERESTS

A. Maniakas declares no competing interests. M. Zafereo: principal investigator for clinical trials funded by Merck and Eli Lilly. M.E. Cabanillas: research funding from Eisai, Exelixis, Kura Oncology, and Genentech; participated in advisory boards for LOXO, Bayer, and Ignyta.

## REFERENCES

1. Lin B, Ma H, Ma M, et al. The incidence and survival analysis for anaplastic thyroid cancer: a SEER database analysis. Am J translational Res 2019;11:5888–96.

2. Maniakas A, Dadu R, Busaidy NL, et al. Evaluation of overall survival in patients with anaplastic thyroid carcinoma, 2000-2019. JAMA Oncol 2020;6:1397–404.
3. Are C, Shaha AR. Anaplastic thyroid carcinoma: biology, pathogenesis, prognostic factors, and treatment approaches. Ann Surg Oncol 2006;13:453–64.
4. Smallridge RC, Marlow LA, Copland JA. Anaplastic thyroid cancer: molecular pathogenesis and emerging therapies. Endocr-related cancer 2009;16:17–44.
5. Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1104–39.
6. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): What Changed and Why? Thyroid 2017;27:751–6.
7. Pozdeyev N, Gay LM, Sokol ES, et al. Genetic Analysis of 779 Advanced Differentiated and Anaplastic Thyroid Cancers. Clin Cancer Res : official J Am Assoc Cancer Res 2018;24:3059–68.
8. Wang JR, Zafereo M, Dadu R, et al. Complete surgical resection following neoadjuvant dabrafenib plus trametinib in BRAFV600E-mutated anaplastic thyroid carcinoma. Thyroid 2019;29(8):1036–43.
9. Xu B, Fuchs T, Dogan S, et al. Dissecting anaplastic thyroid carcinoma: a comprehensive clinical, histologic, immunophenotypic, and molecular study of 360 Cases. Thyroid 2020;30:1505–17.
10. Oishi N, Kondo T, Ebina A, et al. Molecular alterations of coexisting thyroid papillary carcinoma and anaplastic carcinoma: identification of TERT mutation as an independent risk factor for transformation. Mod Pathol 2017;30:1527–37.
11. Bible KC, Kebebew E, Brierley J, et al. 2021 American thyroid association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2021;31:337–86.
12. Janz TA, Neskey DM, Nguyen SA, et al. Is the incidence of anaplastic thyroid cancer increasing: A population based epidemiology study. World J Otorhinolaryngol - Head Neck Surg 2019;5:34–40.
13. Iyer PC, Cote GJ, Hai T, et al. Circulating BRAF V600E Cell-Free DNA as a Biomarker in the Management of Anaplastic Thyroid Carcinoma. JCO Precision Oncol 2018;1–11.
14. Cabanillas ME, Williams MD, Gunn GB, et al. Facilitating anaplastic thyroid cancer specialized treatment: A model for improving access to multidisciplinary care for patients with anaplastic thyroid cancer. Head & neck 2017;39:1291–5.
15. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic braf v600-mutant anaplastic thyroid cancer. J Clin Oncol 2018;36:7–13.
16. Henderson YC, Mohamed ASR, Maniakas A, et al. A high-throughput approach to identify effective systemic agents for the treatment of anaplastic thyroid carcinoma. J Clin Endocrinol Metab 2021;106:2962–78.
17. Maniakas A, Henderson YC, Hei H, et al. Novel anaplastic thyroid cancer PDXs and cell lines: Expanding preclinical models of genetic diversity. J Clin Endocrinol Metab 2021;106(11):e4652–65.
18. Qin Y, Wang JR, Wang Y, et al. Clinical utility of circulating cell-free dna mutations in anaplastic thyroid carcinoma. Thyroid 2021;31:1235–43.
19. Corcoran RB, Chabner BA. Application of Cell-free DNA Analysis to Cancer Treatment. New Engl J Med 2018;379:1754–65.

20. Sandulache VC, Williams MD, Lai SY, et al. Real-time genomic characterization utilizing circulating cell-free dna in patients with anaplastic thyroid carcinoma. Thyroid 2017;27:81–7.
21. Pembrolizumab, Dabrafenib, and Trametinib Before Surgery for the Treatment of BRAF-Mutated Anaplastic Thyroid Cancer. 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04675710.
22. Wang L, Leite de Oliveira R, Huijberts S, et al. An acquired vulnerability of drug-resistant melanoma with therapeutic potential. Cell 2018;173:1413–25.e14.
23. Facchinetti F, Lacroix L, Mezquita L, et al. Molecular mechanisms of resistance to BRAF and MEK inhibitors in BRAF(V600E) non-small cell lung cancer, 132. Oxford, England: European journal of cancer; 2020. p. 211–23, 1990.
24. Villanueva J, Vultur A, Lee JT, et al. Acquired resistance to BRAF inhibitors mediated by a RAF kinase switch in melanoma can be overcome by cotargeting MEK and IGF-1R/PI3K. Cancer Cell 2010;18:683–95.
25. Poulikakos PI, Persaud Y, Janakiraman M, et al. RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF(V600E). Nature 2011;480:387–90.
26. Van Allen EM, Wagle N, Sucker A, et al. The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma. Cancer Discov 2014;4:94–109.
27. Danysh BP, Rieger EY, Sinha DK, et al. Long-term vemurafenib treatment drives inhibitor resistance through a spontaneous KRAS G12D mutation in a BRAF V600E papillary thyroid carcinoma model. Oncotarget 2016;7:30907–23.
28. Owen DH, Konda B, Sipos J, et al. KRAS G12V Mutation in Acquired Resistance to Combined BRAF and MEK Inhibition in Papillary Thyroid Cancer. J Natl Compr Cancer Netw 2019;17:409–13.
29. Cabanillas ME, Dadu R, Iyer P, et al. Acquired Secondary RAS Mutation in BRAF(V600E)-Mutated Thyroid Cancer Patients Treated with BRAF Inhibitors. Thyroid 2020;30:1288–96.
30. Kimura ET, Nikiforova MN, Zhu Z, et al. High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. Cancer Res 2003;63:1454–7.
31. Canon J, Rex K, Saiki AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature 2019;575:217–23.
32. Hallin J, Engstrom LD, Hargis L, et al. The KRAS(G12C) Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients. Cancer Discov 2020;10:54–71.
33. Iyer PC, Dadu R, Gule-Monroe M, et al. Salvage pembrolizumab added to kinase inhibitor therapy for the treatment of anaplastic thyroid carcinoma. J Immunother Cancer 2018;6:68.
34. Cabanillas M, Busaidy N, Dadu R, et al. OR27-6 Combination Vemurafenib (BRAF Inhibitor)/Cobimetinib (MEK Inhibitor)/Atezolizumab (Anti-PDL1 Inhibitor) in BRAF-V600E Mutated Anaplastic Thyroid Cancer (ATC): Initial Safety and Feasibility. J Endocr Soc 2019;3(Suppl 1). OR27-6.
35. Chen H, Luthra R, Routbort MJ, et al. Molecular Profile of Advanced Thyroid Carcinomas by Next-Generation Sequencing: Characterizing Tumors Beyond Diagnosis for Targeted Therapy. Mol Cancer Ther 2018;17:1575–84.
36. Dadu R, Rodriguez Canales J, Wistuba I, et al. Targeting immune system in anaplastic thyroid cancer (ATC): a potential treatment approach. Thyroid 2015;Supplement 1:749.

37. Adam P, Kircher S, Sbiera I, et al. FGF-Receptors and PD-L1 in Anaplastic and Poorly Differentiated Thyroid Cancer: Evaluation of the Preclinical Rationale. Front Endocrinol 2021;12:712107.
38. Capdevila J, Wirth LJ, Ernst T, et al. PD-1 Blockade in Anaplastic Thyroid Carcinoma. J Clin Oncol 2020;38:2620–7.
39. Brauner E, Gunda V, Vanden Borre P, et al. Combining BRAF inhibitor and anti PD-L1 antibody dramatically improves tumor regression and anti tumor immunity in an immunocompetent murine model of anaplastic thyroid cancer. Oncotarget 2016;7:17194–211.
40. Zheng L, Li L, He Q, et al. Response to immunotherapy in a patient with anaplastic thyroid cancer: A case report. Medicine 2021;100:e26138.
41. Nabhan F, Kander E, Shen R, et al. Pembrolizumab in a Patient with Treatment-Naïve Unresectable BRAF-Mutation Negative Anaplastic Thyroid Cancer. Case Rep Endocrinol 2021;2021:5521649.
42. Yang SR, Tsai MH, Hung CJ, et al. Anaplastic Thyroid Cancer Successfully Treated With Radiation and Immunotherapy: A Case Report. AACE Clin case Rep 2021;7:299–302.
43. Lorch JH, Barletta JA, Nehs M, et al. A phase II study of nivolumab (N) plus ipilimumab (I) in radioidine refractory differentiated thyroid cancer (RAIR DTC) with exploratory cohorts in anaplastic (ATC) and medullary thyroid cancer (MTC). J Clin Oncol 2020;38:6513.
44. Gunda V, Gigliotti B, Ashry T, et al. Anti-PD-1/PD-L1 therapy augments lenvatinib's efficacy by favorably altering the immune microenvironment of murine anaplastic thyroid cancer. Int J Cancer 2019;144:2266–78.
45. Dierks C, Seufert J, Aumann K, et al. Combination of Lenvatinib and Pembrolizumab Is an Effective Treatment Option for Anaplastic and Poorly Differentiated Thyroid Carcinoma. Thyroid 2021;31:1076–85.
46. Dierks C, Seufert J, Ruf J, et al. 1915P The lenvatinib/pembrolizumab combination induces long lasting and complete responses in patients with metastatic anaplastic or poorly differentiated thyroid carcinoma: Results from a retrospective study and first results from the prospective phase II ATLEP trial. Ann Oncol 2020;31:S1085.
47. Dierks C, Ruf J, Seufert J, et al. Lenvatinib/Pembrolizumab in Metastasized Anaplastic Thyroid Carcinoma (ATC): Interim results of the ATLEP Trial. Thyroid 2021;31. A-2.
48. Cabanillas ME, Ryder M, Jimenez C. Targeted Therapy for Advanced Thyroid Cancer: Kinase Inhibitors and Beyond. Endocr Rev 2019;40(6):1573–604.
49. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. New Engl J Med 2018;378:731–9.
50. Kelly LM, Barila G, Liu P, et al. Identification of the transforming STRN-ALK fusion as a potential therapeutic target in the aggressive forms of thyroid cancer. Proc Natl Acad Sci USA 2014;111:4233–8.
51. Santoro M, Moccia M, Federico G, et al. RET Gene Fusions in Malignancies of the Thyroid and Other Tissues. Genes 2020;11.
52. Cabanillas M, Drilon A, Farago A, et al. 1916P Larotrectinib treatment of advanced TRK fusion thyroid cancer. Ann Oncol 2020;31:S1086.
53. Waguespack SG, Drilon A, Lin JJ, et al. Long-term Efficacy and Safety of Larotrectinib in Patients with Advanced TRK Fusion-positive Thyroid Carcinoma. Thyroid 2021;31:A–6.
54. Wirth LJ, Sherman E, Robinson B, et al. Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. New Engl J Med 2020;383:825–35.

55. Subbiah V, Hu MI, Wirth LJ, et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. Lancet Diabetes Endocrinol 2021;9:491–501.
56. Isham CR, Bossou AR, Negron V, et al. Pazopanib enhances paclitaxel-induced mitotic catastrophe in anaplastic thyroid cancer. Sci translational Med 2013;5:166ra3.
57. Sherman EJ, Harris J, Bible KC, et al. 1914MO Randomized phase II study of radiation therapy and paclitaxel with pazopanib or placebo: NRG-RTOG 0912. Ann Oncol 2020;31:S1085.
58. Takahashi S, Kiyota N, Yamazaki T, et al. A Phase II study of the safety and efficacy of lenvatinib in patients with advanced thyroid cancer. Future Oncol (London, England) 2019;15:717–26.
59. Wirth LJ, Brose MS, Sherman EJ, et al. Open-Label, Single-Arm, Multicenter, Phase II Trial of Lenvatinib for the Treatment of Patients With Anaplastic Thyroid Cancer. J Clin Oncol 2021;39:2359–66.
60. Savvides P, Nagaiah G, Lavertu P, et al. Phase II trial of sorafenib in patients with advanced anaplastic carcinoma of the thyroid. Thyroid 2013;23:600–4.
61. Bible KC, Suman VJ, Menefee ME, et al. A multiinstitutional phase 2 trial of pazopanib monotherapy in advanced anaplastic thyroid cancer. J Clin Endocrinol Metab 2012;97:3179–84.