

Systemic Treatment of Thyroid Cancer: ASCO Guideline

Nabil F. Saba, MD¹ ; Nofisat Ismaila, MD² ; Douglas Adkins, MD³ ; Nishant Agrawal, MD⁴; Neil Akhave, MD⁵ ; Erik S. Blomain, MD, PhD⁶; Maria E. Cabanillas, MD⁵ ; Amy Chen, MD⁷; Thomas J. Galloway, MD⁸; Guilherme Harada, MD⁹ ; Dapeng Li, MD¹⁰ ; Salem I. Noureldine, MD¹¹; Joe Scharpf, MD¹²; Lova L. Sun, MD¹³ ; Mei Tang, MD¹⁴; Lori Wirth, MD¹⁵ ; Francis Worden, MD¹⁶; Dan P. Zandberg, MD¹⁷ ; and Beth M. Beadle, MD¹⁸ 

DOI <https://doi.org/10.1200/JCO-26-00235>

ABSTRACT

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the *ASCO Guidelines Methodology Manual*. ASCO Guidelines follow the *ASCO Conflict of Interest Policy for Clinical Practice Guidelines*.

Clinical Practice Guidelines and other guidance (“Guidance”) provided by ASCO is not a comprehensive or definitive guide to treatment options. It is intended for voluntary use by clinicians and should be used in conjunction with independent professional judgment. Guidance may not be applicable to all patients, interventions, diseases, or stages of diseases. Guidance is based on review and analysis of relevant literature and is not intended as a statement of the standard of care. ASCO does not endorse third-party drugs, devices, services, or therapies and assumes no responsibility for any harm arising from or related to the use of this information. See complete disclaimer in *Appendix 1* and *Appendix 2* (online only) for more.

PURPOSE To provide evidence-based recommendations on the use of systemic therapy in different types of thyroid cancers.

METHODS The American Society of Clinical Oncology convened a multidisciplinary Expert Panel to evaluate the evidence and formulate recommendations. The literature search included studies published between January 1, 2000, and November 5, 2025, and comprised systematic reviews, meta-analyses, randomized controlled trials, and observational studies. Outcomes of interest included overall survival, disease-free survival, and safety. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations.

RESULTS A total of 66 publications were identified to inform the evidence base for this guideline.

RECOMMENDATIONS Evidence-based recommendations address the use of systemic therapy in patients with well-differentiated, differentiated high-grade or poorly differentiated, anaplastic, and medullary thyroid cancer. Additional information is available at <https://ascopubs.org/topics/asco-guidelines/head-neck-cancer>.

ACCOMPANYING CONTENT

 Listen to the podcast by Brittany Harvey and Dr Saba at <https://ascopubs.org/do/systemic-treatment-thyroid-cancer-guideline>

 Appendix

 Data Supplement

Accepted February 11, 2026

Published April 1, 2026

Evidence Based Medicine

Committee approval: January 7, 2026

J Clin Oncol 44:1349-1372

© 2026 by American Society of Clinical Oncology



View Online Article

INTRODUCTION

The treatment of thyroid cancers poses a complex clinical challenge, with outcomes that vary widely depending on tumor histology, molecular profile, prior treatments, and disease burden; multidisciplinary evaluation with surgery, radiation therapy, endocrinology, and medical oncology is crucial for optimal outcomes. Although differentiated thyroid carcinoma is often indolent and highly responsive to surgery and radioiodine therapy, a subset of patients develops progressive, radioiodine-refractory disease that

necessitates the consideration of systemic therapy. Medullary and anaplastic thyroid cancers, by contrast, typically have a more aggressive course and require distinct systemic therapeutic strategies. Differentiated high-grade thyroid carcinoma (DHGTC) or poorly differentiated thyroid carcinoma (PDTC) is a less common subtype characterized by a paucity of clinical data and intermediate biological behavior, with lower responsiveness to conventional therapies; optimal therapy for these malignancies is often extrapolated from other studies. Over the past decade, advances in molecularly targeted therapies, multikinase inhibitors (MKIs),

TARGET POPULATION AND AUDIENCE

Target Population

Patients with well-differentiated, differentiated high-grade or poorly differentiated, anaplastic, and medullary thyroid cancer.

Target Audience

Medical oncologists, radiation oncologists, head and neck surgeons, endocrinologists, other physicians, oncology nurses, advanced nurse practitioners, nurse navigators, allied health professionals, clinical researchers, health policy researchers, and patients with head and neck cancer.

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix [Table A1](#), online only).

The recommendations were developed by using a systematic review of evidence identified through online searches of PubMed (January 1, 2000, through November 5, 2025) for phase III randomized controlled trials (RCTs), and observational studies. Articles were selected for inclusion in the systematic review based on the following criteria:

- Population: Patients with well-differentiated, DHGTC or PDTC, anaplastic, and medullary thyroid cancer (MTC).
- Interventions: vascular endothelial growth factor tyrosine kinase inhibitors (TKIs), targeted therapies for *BRAF* V600E mutation, *RET* mutation, *RET* fusion, *NTRK* fusion, *ROS1* fusion, *ALK* fusion, immune checkpoint inhibitors, and cytotoxic chemotherapy.
- Comparisons: Placebo, observation.
- Outcomes: Overall survival (OS), disease-free survival, and safety.
- Sample size: Minimum sample size of 10.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language.

Three full-panel meetings and multiple subgroup meetings were held, and members were asked to provide ongoing input on the guideline development protocol, quality and assessment of the evidence, generation of recommendations, draft content, as well as review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the Expert Panel co-chairs and corresponded with the Panel via e-mail and virtual meetings to coordinate the process to completion. Ratings for the strength of the recommendation and evidence quality are provided with each recommendation, defined in Appendix [Table A2](#). The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.^{3,4} GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel. All funding for the administration of the project was provided by ASCO.

and immunotherapy have reshaped the management landscape of thyroid cancers, offering improved disease control but also introducing new considerations in sequencing of agents and toxicity, as well as integration into multidisciplinary care.¹ The recent approval of MKIs, BRAF-, RET-, and NTRK-targeted agents, and selective use of immunotherapy expanded the therapeutic armamentarium,² although questions remain regarding appropriate use and sequencing of these agents. The purpose of this guideline is to provide evidence-based, consensus-driven recommendations in the use of systemic therapy for different types of thyroid cancers with the goal of optimizing therapeutic decision making, standardizing care across diverse clinical settings, and identifying opportunities for future trials and approaches.

The evidence base for any clinical practice recommendations is built on the characteristics of the patients who participated in the underlying studies. Broad enrollment in clinical trials is essential for clinicians to assess the generalizability of trial results and understand safety and efficacy across populations.

GUIDELINE QUESTIONS

This clinical practice guideline addresses four overarching clinical questions for each of the thyroid cancer disease subtypes (well-differentiated, DHGTC or PDTC, anaplastic, and medullary): (1) Do MKIs compared to placebo or observation impact survival and what should be recommended in the first-line and subsequent-line setting? (2) Do genomically targeted therapies compared to placebo or observation impact survival in the first-line and subsequent-line setting? (3) Does immunotherapy compared to targeted agents or MKIs impact response and/or survival in the first-line and subsequent-line setting? (4) Does cytotoxic chemotherapy compared to targeted agents or MKIs impact response and/or survival in the first-line and subsequent-line setting?

Guideline Review and Approval

The draft recommendations were released to the public for open comment from July 17 through 30, 2025. Response categories of “Agree as written,” “Agree with suggested modifications,” and “Disagree. See comments” were captured for every proposed recommendation with 11 respondents and 21 written comments received. Of the 32 recommendations included in the open comment, only 2% of the responses disagreed with a recommendation, while the remaining 98% either agreed or agreed with slight modifications to the recommendations. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions.

All changes were incorporated into the final manuscript before ASCO Evidence Based Medicine Committee (EBMC) review and approval. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO EBMC before submission to the *Journal of Clinical Oncology* for editorial review and consideration for publication.

Guideline Updating

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guidelines. Based on formal review of emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 1,146 articles were identified in the literature search. After applying the eligibility criteria, 66 articles remained, forming the evidentiary basis for the guideline recommendations.^{5-30,31-50,51-72}

The identified trials were published between 2010 and 2025. The studies looked at interventions, including MKIs, genomically targeted therapy, immunotherapy, and chemotherapy in patients with radioiodine refractory differentiated, DHGTC or PDTC, anaplastic, and medullary thyroid cancers. The outcomes included OS, progression-free survival (PFS), objective response rate (ORR), and safety. The summary of the characteristics of studies by intervention is included in [Table 1](#). Further characteristics of the studies' participants and systematic review flow diagram are provided in the Data Supplement.

Evidence Quality Assessment

The quality of evidence was assessed for each outcome of interest. This rating includes factors such as study design, consistency of results, directness of evidence, precision, publication bias, and magnitude of effect, assessed by one reviewer. Evidence quality ratings for the outcomes of interest are provided in the supplement. Refer to [Appendix Table A2](#) for definitions for the quality of the evidence, and the Methodology Manual for more information.

RECOMMENDATIONS

All recommendations are available in [Table 2](#), and [Figures 1-4](#) show the recommendations as algorithms.

WELL-DIFFERENTIATED

The primary treatment of well-differentiated thyroid cancer is surgery with or without radioactive iodine (RAI) therapy. In the event of recurrence, multidisciplinary management of these cases is recommended, including evaluation for further therapy with surgery, RAI, and/or external-beam radiotherapy. The following recommendations pertain to systemic therapy recommendations for radioiodine-refractory recurrent or metastatic disease after primary treatment.

Question 1

In patients with RAI-refractory well-differentiated thyroid cancer (papillary, follicular, oncocytic), do MKIs compared to placebo or observation impact survival and what should be recommended in the first-line and subsequent-line setting?

Recommendation 1.1

Literature review and analysis. The double blind phase III SELECT trial by Schlumberger et al⁴⁵ randomly assigned 261 patients to receive lenvatinib (at a once daily dose of 24 mg per day in 28-day cycles) and 131 patients to receive placebo. The study reported a median PFS of 18.3 months with lenvatinib v 3.6 months with placebo (hazard ratio [HR] for progression or death, 0.21 [95% CI, 0.14 to 0.31]; $P < .001$). The ORR was 64.8% with lenvatinib and 1.5% with placebo ($P < .001$), and the median duration of response to lenvatinib was 30 months (95% CI, 18.4 to 36.7). In the double-blind phase III DECISION trial of sorafenib versus placebo by Brose et al,⁴⁴ patients were randomly allocated on a 1:1 basis to sorafenib or placebo with the intention-to-treat population comprising 417 patients (207 in the sorafenib group and 210 in the placebo group). Median PFS was 10.8 months with sorafenib and 5.8 months with placebo (HR, 0.59 [95% CI, 0.45 to 0.76]; $P < .0001$).⁴⁴ The ORR was 12.2% in the sorafenib arm, compared to 0.5% for those treated with placebo ($P < .0001$). Generally, lenvatinib is the preferred first-line

TABLE 1. Characteristics of Studies Identified in the Literature Search

Topic	Multikinase Inhibitors	Genomically Targeted Therapy	Immunotherapy	Chemotherapy	Total
Well-differentiated	9 SR/MA ¹²⁻²⁰	1 SR/MA ⁷ 1 Phase II/III RCT ⁸ 3 Single-arm Phase I/II ⁹⁻¹¹	1 Phase II/III RCT ⁵ 1 Single-arm phase I/II ⁶	0	16
Differentiated high-grade or poorly differentiated	2 Phase II/III RCT ^{44,45} 1 Single-arm Phase I/II ⁴⁶	0	0	0	3
Anaplastic	1 SR/MA ⁶⁰ *5 Single-arm Phase I/II ^{35,38,61-66} 6 Retrospective ⁶⁷⁻⁷²	5 Single-arm Phase I/II ⁵¹⁻⁵⁵ 4 Retrospective ⁵⁶⁻⁵⁹	*1 Single-arm Phase I/II ⁵ 1 Retrospective ⁵⁰	1 Phase II/III RCT ⁴⁷ 2 Retrospective ^{48,49}	25
Medullary	1 SR/MA ^{13,30} 4 Phase II/III RCT ³¹⁻³⁴ 7 Single-arm Phase I/II ³⁵⁻⁴¹ 2 Retrospective studies ^{42,43}	2 Phase II/III RCT ^{21,22} 4 Single-arm Phase I/II ²³⁻²⁷ 2 Retrospective studies ^{28,29}	0	0	22
Total	38	22	3	3	66

Abbreviations: MA, meta-analysis; RCT, randomized controlled trial; SR, systematic review.

regimen due to its higher response rate and longer PFS compared to sorafenib in these landmark studies.

Clinical interpretation. The results of prospective, randomized, placebo-controlled studies confirm the benefit of treatment with multikinase TKIs in patients with RAI-refractory, well-differentiated thyroid cancer. Most patients who require treatment for their disease are symptomatic and need a reduction in tumor burden. Since the response rates for lenvatinib are almost three times that of sorafenib, lenvatinib is generally the preferred first-line agent. Similarly, PFS is longer with lenvatinib. However, head-to-head studies comparing the efficacy of these two agents are lacking. Both lenvatinib and sorafenib were associated with significant adverse effects that often led to dose reductions and discontinuation of therapy in their respective randomized, placebo-controlled trials. In general, sorafenib is associated with increased hand-foot skin reactions and diarrhea. Lenvatinib, on the other hand, causes more frequent hypertension, weight loss, and proteinuria. Thus, the patient's existing comorbidities and ability to tolerate treatment should be considered when selecting lenvatinib or sorafenib as first-line therapy. Moreover, patients with preexisting uncontrolled hypertension, who are at higher risk for cardiovascular events, may be more suitable for treatment with sorafenib. Whether either agent is selected, close monitoring is required to institute drug holds, treat adverse reactions, and reduce dosages when appropriate.

Recommendation 1.2

Literature review and analysis. In the global phase III RCT (COSMIC-311) by Brose et al,⁷³ patients were randomly assigned to cabozantinib (n = 125) or placebo (n = 62). A significant improvement in PFS with cabozantinib was reported over placebo (11.0 months v 1.9 months; HR, 0.22; $P < .0001$) in patients who had disease progression on a prior multitargeted TKI (lenvatinib or sorafenib). The benefit was

observed across all histologic variants whether treated with sorafenib or lenvatinib upfront. Similarly, disease control rates improved with cabozantinib over placebo. A modest response of 15% was seen with cabozantinib compared to a 0% response rate with placebo.

Clinical interpretation. While other MKIs may be considered as second-line therapy, cabozantinib is the preferred agent since COSMIC-311 is the only published randomized study demonstrating clinical benefit. Hypertension, palmar-plantar erythrodysesthesia, and fatigue are the most common side effects associated with cabozantinib, all of which are manageable with supportive care, dose holding, and reductions. Preexisting, poorly controlled hypertension, or renal dysfunction may preclude its use due to concerns for developing cardiovascular disease and proteinuria.

Question 2

In patients with RAI-refractory, well-differentiated thyroid cancer (papillary, follicular, oncocyctic), do genomically targeted therapies compared to placebo or observation impact survival and what should be recommended in the first-line and subsequent-line setting?

Recommendation 2.1

Literature review and analysis. Genomic testing should be performed to evaluate alterations that may confer benefit from a personalized treatment strategy with targeted therapies. Several selective inhibitors, including entrectinib, larotrectinib, and repotrectinib for *NTRK* gene fusions, pralsetinib and selpercatinib for *RET* fusions, and dabrafenib or the combination of dabrafenib plus trametinib for *BRAF* V600E mutations, may be offered as first-line treatment. The data to support the use of these agents come from multi-institutional randomized (dabrafenib v dabrafenib plus trametinib)⁸ and nonrandomized studies (pralsetinib and

TABLE 2. Summary of All Recommendations

Clinical Question	Recommendation
<i>General Note.</i> The following recommendations (strong or conditional) and terminology (see the Data Supplement) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible.	
WELL-DIFFERENTIATED (papillary, follicular, oncocytic) Notes: <i>The primary treatment of well-differentiated thyroid cancer is surgery with or without radioactive iodine therapy</i> <i>The following recommendations pertain to recurrent or metastatic disease after primary treatment.</i>	
1. In patients with RAI-refractory, well-differentiated thyroid cancer, do multikinase inhibitors (MKIs) compared to placebo/observation impact survival in the first- and subsequent-line setting?	1.1. For patient populations in the first-line setting, clinicians should offer lenvatinib or sorafenib. (Evidence quality: High; Strength of recommendation: Strong) <i>Qualifying Statement for Recommendation 1.1:</i> Although both drugs are approved as first-line options, and despite the lack of direct comparative evidence, lenvatinib would be considered first choice due to the best available efficacy evidence. 1.2. For patient populations in the subsequent-line setting, clinicians should offer cabozantinib. (Evidence quality: High; Strength of recommendation: Strong)
2. In patients with RAI-refractory, well-differentiated thyroid cancer, do genomically targeted therapies compared to placebo/observation impact survival in the first- and subsequent-line setting?	2.1. For patient populations with genomic alterations in the first-line setting, clinicians may offer genomically targeted therapy. (Evidence quality: Moderate; Strength of recommendation: Strong) 2.1.1. For patient populations in the first-line setting, whose tumor harbors <i>NTRK</i> or <i>RET</i> fusions, clinicians should offer genomically targeted therapies (larotrectinib or entrectinib for <i>NTRK</i>, selpercatinib for <i>RET</i>) prior to treatment with MKIs. (Evidence quality: Moderate; Strength of recommendation: Strong) 2.1.2. For patient populations in the first-line setting, whose tumor harbors a <i>BRAF</i> V600E mutation, clinicians may offer genomically targeted therapies (dabrafenib or trametinib) prior to treatment with MKIs. (Evidence quality: Low; Strength of recommendation: Conditional) 2.2. For patient populations with genomic alterations in the subsequent-line setting, who have been previously treated with MKIs, clinicians should offer genomically targeted therapies (<i>NTRK</i>, <i>BRAF</i> V600E, or <i>RET</i> inhibitors). (Evidence quality: Moderate; Strength of recommendation: Strong)
3. In patients with RAI-refractory, well-differentiated thyroid cancer, does immunotherapy compared to targeted agents or MKIs impact response and/or survival in the first- and subsequent-line setting?	3.1. For patient populations in the first-line setting, clinicians should not offer immunotherapy outside of a clinical trial. (Evidence quality: Moderate; Strength of recommendation: Strong) 3.2. For patient populations in the subsequent-line setting, clinicians may add pembrolizumab to lenvatinib to patients who have disease progression on lenvatinib alone. (Evidence quality: Low; Strength of recommendation: Conditional)
4. In patients with RAI-refractory, well-differentiated thyroid cancer, does cytotoxic chemotherapy compared to targeted agents or MKIs impact response and/or survival in the first- and subsequent-line setting?	4.1. For patient populations in the first-line setting, clinicians should not offer cytotoxic chemotherapy outside of a clinical trial. (Evidence quality: Low; Strength of recommendation: Strong) 4.2. For patient populations in the subsequent-line setting, who have disease progression on genomically targeted therapies and MKIs, clinicians may offer treatment with cytotoxic chemotherapy. (Evidence quality: Low; Strength of recommendation: Conditional)
DIFFERENTIATED HIGH-GRADE (DHGTC) or POORLY DIFFERENTIATED (PDTC) Notes: <i>The data on DHGTC or PDTC as an independent entity are limited. The data are largely derived from subgroup analyses from studies focused on either well-differentiated or anaplastic cancers.</i> <i>The primary treatment of DHGTC or PDTC is surgery with or without radioactive iodine therapy.</i> <i>The following recommendations pertain to recurrent or metastatic disease after primary treatment.</i>	
5. In patients with RAI-refractory DHGTC or PDTC, do MKIs compared to placebo/observation impact survival in the first- and subsequent-line setting?	5.1. For patient populations in the first-line setting, clinicians may offer lenvatinib or sorafenib. (Evidence quality: Moderate for lenvatinib, Low for sorafenib; Strength of recommendation: Conditional) <i>Qualifying Statement for Recommendation 5.1:</i> Although both drugs are approved as first-line options, and despite the lack of direct comparative evidence, lenvatinib would be considered first choice due to the best available efficacy evidence. 5.2. For patient populations in the subsequent-line setting, there are insufficient data to recommend for or against the use of MKIs. (Evidence quality: Low; Strength of recommendation: Conditional)
6. In patients with RAI-refractory DHGTC or PDTC, do genomically targeted therapies compared to placebo/observation impact survival in the first- and subsequent-line setting?	6.1. For patient populations in the first- or subsequent-line settings, if their tumors harbor actionable genomic alterations, genomically targeted therapies may be offered. (Evidence quality: Low; Strength of recommendation: Conditional) <i>Qualifying Statement for Recommendation 6.1:</i> Due to the lack of robust clinical trial data specifically supporting the use of these agents in this particular setting, there is insufficient evidence to formally recommend for or against their routine use at this time.

(continued on following page)

TABLE 2. Summary of All Recommendations (continued)

Clinical Question	Recommendation
7. In patients with RAI-refractory DHGTC or PDTC, does immunotherapy compared to targeted agents or MKIs impact response and/or survival in the first- and subsequent-line setting?	7.1. For patient populations in the first- or subsequent-line settings, immunotherapy (such as PD-1 or PD-L1 inhibitors) may be offered as a treatment option. (Evidence quality: Low; Strength of recommendation: Conditional) <i>Qualifying Statement for Recommendation 7.1:</i> Due to the insufficient clinical data from dedicated trials in the PDTC population, there is no formal recommendation for or against the routine use of immunotherapy in this setting.
8. In patients with RAI-refractory DHGTC or PDTC, does cytotoxic chemotherapy compared to targeted agents or MKIs impact response and/or survival in the first- and subsequent-line setting?	8.1. For patient populations in the first- or subsequent-line settings, there are insufficient data to recommend for or against the use of cytotoxic chemotherapy. (Evidence quality: Low; Strength of recommendation: Conditional)
ANAPLASTIC Notes: <i>Anaplastic thyroid cancer requires a multidisciplinary approach to therapy including surgery, radiation, systemic therapy, and airway management. The following recommendations pertain to the use of systemic therapy at initial diagnosis or following primary therapy.</i>	
9. In patients with anaplastic thyroid cancer, do MKIs compared to placebo/observation impact survival in the first- and subsequent-line setting?	9.1. For patient populations with ATC without a genomic mutation in the first-line setting, clinicians may offer lenvatinib. (Evidence quality: Very Low; Strength of recommendation: Conditional) <i>Qualifying Statement for Recommendation 9.1:</i> Pembrolizumab may be added to lenvatinib based on results from a prospective study. 9.2. For patient populations with ATC without a genomic mutation in the subsequent-line setting, who have disease progression on lenvatinib or lenvatinib + pembrolizumab, participation in a clinical trial is recommended, given the lack of evidence supporting the use of other agents. (Evidence quality: Low; Strength of recommendation: Conditional)
10. In patients with anaplastic thyroid cancer, do genomically targeted therapies compared to placebo/observation impact survival in the first- and subsequent-line setting?	10.1. For patient populations with <i>BRAF</i> V600E–mutated ATC in the first-line setting, clinicians should offer <i>BRAF</i> or <i>MEK</i> inhibitor targeted therapy (dabrafenib and trametinib). (Evidence quality: Moderate; Strength of recommendation: Strong) 10.1.1. For patient populations with <i>BRAF</i> V600E–mutated ATC in the first-line setting, clinicians may offer <i>BRAF</i> or <i>MEK</i> inhibitor targeted therapy (dabrafenib and trametinib) + pembrolizumab. (Evidence quality: Low; Strength of recommendation: Conditional) 10.2. For patient populations in the first-line setting, whose tumor harbors <i>NTRK</i> or <i>RET</i> fusions, clinicians may offer <i>NTRK</i> or <i>RET</i> targeted therapy (larotrectinib or entrectinib for <i>NTRK</i>, selipergatinib for <i>RET</i>). (Evidence quality: Very Low; Strength of recommendation: Conditional) 10.3. For patient populations in the subsequent-line setting whose disease progressed on genomically targeted therapy, participation in clinical trials is recommended. If not available, lenvatinib may be offered. (Evidence quality: Very Low; Strength of recommendation: Conditional) <i>Qualifying Statement for Recommendation 10.3:</i> Pembrolizumab may be added to lenvatinib based on results from a prospective study.
11. In patients with anaplastic thyroid cancer, does immunotherapy impact response and/or survival in the first- and subsequent-line setting?	11.1. For patient populations with ATC without a genomic mutation in the first-line setting, clinicians may offer lenvatinib + pembrolizumab or ipilimumab + nivolumab. (Evidence quality: Low; Strength of recommendation: Conditional) 11.2. For patient populations with <i>BRAF</i> V600E–mutated ATC in the subsequent-line setting, clinicians may offer pembrolizumab, in combination with dabrafenib + trametinib. (Evidence quality: Low; Strength of recommendation: Conditional)
12. In patients with anaplastic thyroid cancer, does cytotoxic chemotherapy compared to targeted agents or MKIs impact response and/or survival in the first- and subsequent-line setting?	12.1. For patient populations in the first-line setting who are candidates for genomically targeted therapy or MKIs, clinicians should not offer cytotoxic chemotherapy outside of a clinical trial. (Evidence quality: Low; Strength of recommendation: Strong) 12.2. For patient populations in the subsequent-line setting, who have disease progression on genomically targeted therapies, MKIs, and immunotherapy, clinicians may offer cytotoxic chemotherapy. (Evidence quality: Low; Strength of recommendation: Conditional)
MEDULLARY Notes: <i>The primary treatment of medullary thyroid cancer is surgery. The following recommendations pertain to recurrent or metastatic disease after primary treatment.</i>	

(continued on following page)

TABLE 2. Summary of All Recommendations (continued)

Clinical Question	Recommendation
13. In patients with medullary thyroid cancer, do MKIs compared to placebo/observation impact survival in the first- and subsequent-line setting?	13.1. For patient populations with <i>RET</i> wild-type disease in the first-line setting, clinicians should offer cabozantinib or vandetanib. (Evidence quality: High; Strength of recommendation: Strong) 13.2. For patient populations with <i>RET</i> wild-type disease in the subsequent-line setting, who have disease progression on cabozantinib or vandetanib, participation in clinical trials is recommended. If not available, patients with disease that progressed on cabozantinib may be offered vandetanib or vice versa. (Evidence quality: Low; Strength of recommendation: Conditional)
14. In patients with medullary thyroid cancer, do genomically targeted therapies compared to placebo/observation impact survival in the first- and subsequent-line setting?	14.1. For patient populations with <i>RET</i> mutant disease in the first-line setting, clinicians should offer selpercatinib. (Evidence quality: High; Strength of recommendation: Strong) 14.2. For patient populations with <i>RET</i> mutant disease in the subsequent-line setting, who have disease progression on selpercatinib, participation in clinical trials is recommended. If not available, patients may be offered vandetanib or cabozantinib. (Evidence quality: Low; Strength of recommendation: Conditional)
15. In patients with medullary thyroid cancer, does immunotherapy compared to targeted agents or MKIs impact response and/or survival in the first- and subsequent-line setting?	15.1. For patient populations in the first- and subsequent-line setting, clinicians should not offer immunotherapy outside of a clinical trial. (Evidence quality: Low; Strength of recommendation: Strong)
16. In patients with medullary thyroid cancer, does cytotoxic chemotherapy compared to targeted agents or MKIs impact response and/or survival in the first- and subsequent-line setting?	16.1. For patient populations in the first-line setting, clinicians should not offer cytotoxic chemotherapy outside of a clinical trial. (Evidence quality: Low; Strength of recommendation: Strong) 16.2. For patient populations in the subsequent-line setting, whose disease progressed on genomically targeted therapies and MKIs, clinicians may offer treatment with cytotoxic chemotherapy. (Evidence quality: Low; Strength of recommendation: Conditional)

NOTE. The strength of the recommendation is defined as follows: Strong: In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention. Conditional: In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

Abbreviations: ATC, anaplastic thyroid cancer; DHGTC, differentiated high-grade thyroid cancer; MKI, multikinase inhibitor; PDTC, poorly differentiated thyroid cancer; PFS, progression-free survival; RAI, radioactive iodine.

selpercatinib)^{24,27} as well as pooled analyses (entrectinib, larotrectinib, and repotrectinib).⁷

Clinical interpretation. Deep and durable response rates with long progression-free intervals and more tolerable side-effect profiles support the use of genomically targeted therapies upfront. Unlike the MKIs (lenvatinib and sorafenib), which may also be considered as first-line therapy for tumors harboring driver alterations, no randomized, placebo-controlled studies with genomically targeted therapies have been conducted.

Recommendation 2.1.1

Literature review and analysis. For tumors with *NTRK* gene fusions, in a pooled analysis of phase I/II trials, larotrectinib produced an 86% ORR (95% CI, 64 to 97; N = 22).⁷⁴ The median response time was 1.9 months, and the median duration of response was between 35 and 43 months for patients with RAI-refractory, differentiated thyroid cancer. The median PFS ranged from 39 to 44 months, and the 6-year OS rate was 71% (95% CI, 50 to 91). Similarly, entrectinib demonstrated substantial activity in thyroid cancer with an overall response rate of 57% (95% CI, 43.2 to

70.8) in a pooled analysis of phase I/II trials (N = 54).⁷⁵ Additionally, the median time to response was 1.8 months and the median duration of response 10 to 20 months, with a median PFS of 13.8 months.

Repotrectinib is a next-generation, macrocyclic tropomyosin receptor kinase inhibitor approved for the treatment of solid tumors with *NTRK* gene fusions, including differentiated thyroid cancers. This agent was designed to overcome resistance mutations, including solvent-front, gatekeeper, and xDFG mutations, all of which can develop during treatment with first-generation *NTRK* inhibitors (larotrectinib and entrectinib). This agent was granted accelerated approval in 2024 on the basis of the TRIDENT-1 study, which demonstrated an ORR of 79% (95% CI, 68 to 88) in TKI-naïve patients, with median duration of response 34.1 months (95% CI, 25.6 to not estimable [NE]) and median PFS 35.7 months (95% CI, 27.4 to NE). While thyroid cancer was represented in the study, these patients only comprised about 3% of the study population (n = 11),⁷⁶ indicating that more targeted study of response in this population may be warranted.

For patients with tumors harboring *RET* fusions (n = 19), a phase I/II trial with selpercatinib reported an ORR of 79%

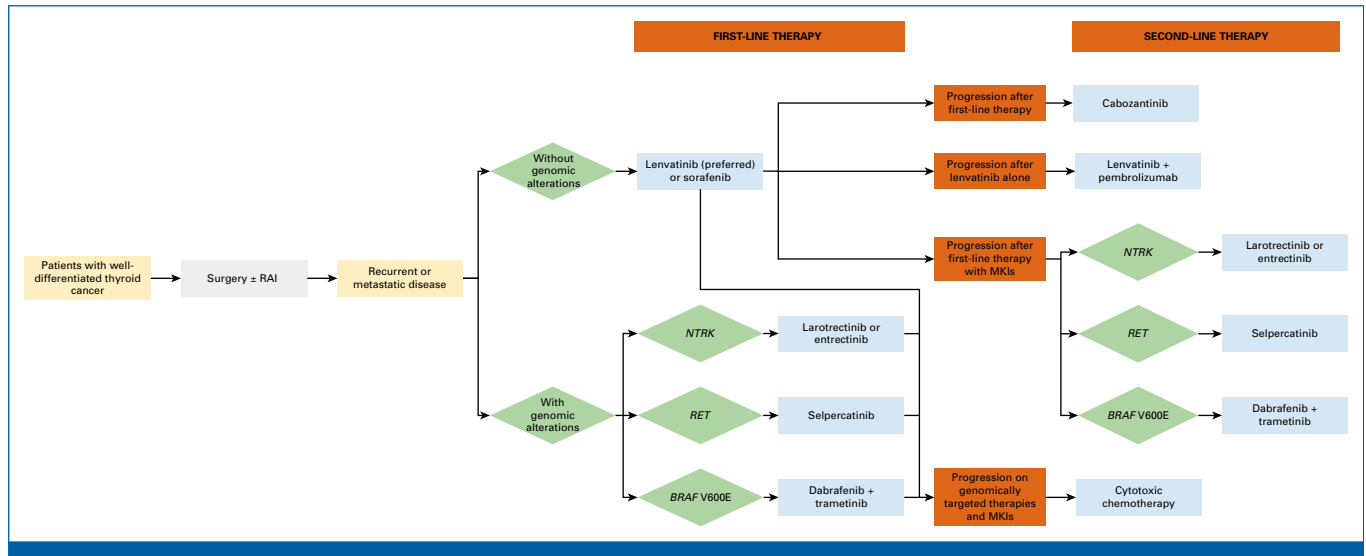


FIG 1. Systemic treatment of well-differentiated thyroid cancer algorithm. MKI, multikinase inhibitor; RAI, radioactive iodine.

(95% CI, 54 to 94).²⁶ Patients who were previously treated experienced durable responses. At 1 year, 71% of responses were ongoing, and 64% of patients were progression-free. In the treatment-naïve population, the median PFS was not reached at a median follow-up of 30.4 months, and the 3-year PFS rate was 87.3%. Similarly, in a phase I/II trial with pralsetinib, the overall response rate in patients previously treated was 91% (95% CI, 71 to 99) with a median duration of response of 17.5 months and median PFS between 19.4 and 25.4 months.²⁴ In the treatment-naïve population, the overall response rate was 89% (95% CI, 52 to 100), and the median PFS was not reached at a median follow-up of 21.5 months.

Clinical interpretation. Rapid and longstanding responses were seen for both larotrectinib and entrectinib, irrespective of treatment with prior systemic therapy. With the ability of NTRK inhibitors to cross the blood-brain barrier, durable activity was also detected in patients with CNS metastases. In general, few patients experienced grade 3-4 treatment-related adverse events with low rates of discontinuation for either agent. Due to their striking efficacy and tolerability, and despite the lack of randomized trials comparing these agents to MKIs, larotrectinib or entrectinib should be offered in the first line for patients with

NTRK fusion-positive differentiated thyroid cancer when therapy is required. While no head-to-head comparisons have been conducted, larotrectinib may be the preferred therapy since the response rate and progression-free interval of this agent are more pronounced. Once acquired resistance develops on one of the first-generation NTRK inhibitors, treatment with repotrectinib should be considered.

Similar to treatment with NTRK inhibitors, RET fusion inhibitors produce deep, sustained responses with long progression-free intervals. Both selpercatinib and pralsetinib are well tolerated with patients experiencing primarily grade 1-2 treatment-related toxicity. Only 2%-5% of patients discontinued study with either agent, and both cross the blood-brain barrier. Currently, either selpercatinib or pralsetinib should be offered as first-line therapy for patients with RET fusion-positive differentiated thyroid cancer.

Recommendation 2.1.2

Literature review and analysis. In a nonrandomized, multicenter phase II trial involving 26 previously untreated

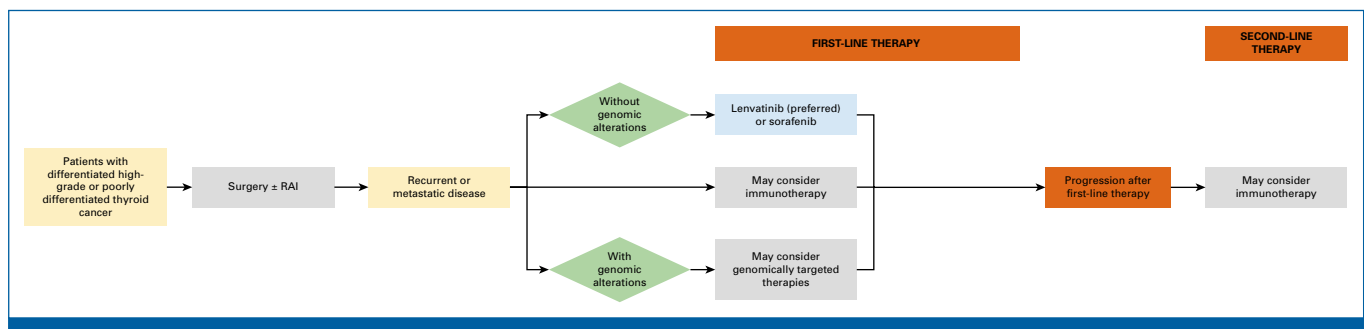


FIG 2. Systemic treatment of differentiated high-grade or poorly differentiated thyroid cancer algorithm. RAI, radioactive iodine.

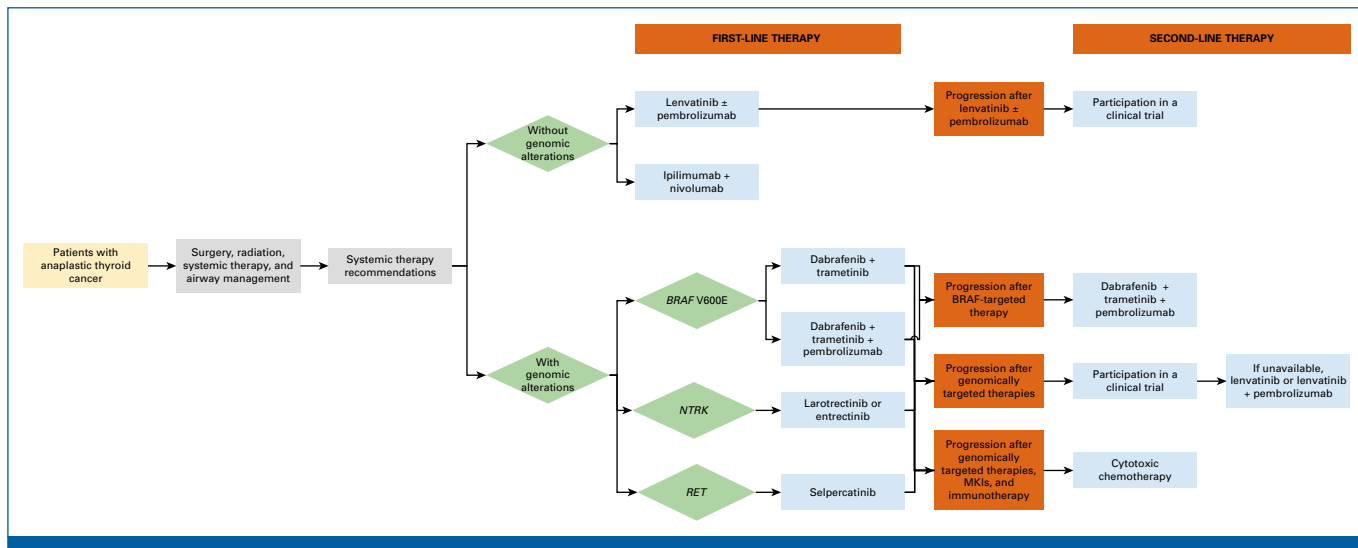


FIG 3. Systemic treatment of anaplastic thyroid cancer algorithm. MKI, multikinase inhibitor.

patients with *BRAF* V600E mutation–positive papillary thyroid cancer, single-agent vemurafenib demonstrated significant antitumor activity. The trial reported a partial response rate of 38.5% (95% CI, 20% to 59%). With a median follow-up of 19 months, the median duration of response was 16.5 months (5.7 to NE), the median PFS was 18.2 months (95% CI, 15.5 to 29.3), and the median OS was not yet reached (NE to NE).¹⁰

In a phase II, multicenter study, patients with *BRAF* V600E–mutated, RAI-refractory thyroid cancers were randomly assigned to dabrafenib alone versus dabrafenib plus trametinib. The ORR by RECIST 1.1 was 42% (95% CI, 23% to 63%) for dabrafenib and 48% (95% CI, 29% to 68%) for dabrafenib plus trametinib ($P = .67$). With a median follow-up time of 23 months, the median response duration was 18.3 months (95% CI, 5.0 to NE) for dabrafenib and 17 months for the combination arm (95% CI, 9.7 to 44.5); the PFS was 10.7 months (95% CI, 3.8 to 34.7) for dabrafenib alone and 15.1 months (95% CI, 12.3 to 37.3) for the combination therapy. Skin reactions, fatigue, fevers, and

hyperglycemia were the most common toxicities reported with single-agent therapy or the combination.⁸

Clinical interpretation. In addition to PFS, response rate becomes an important end point when selecting patients for treatment since many are symptomatic and require a reduction in tumor burden. Response rates for *BRAF* V600E inhibitors as single agents or in combination with a MEK inhibitor range from 30% to 38% in the frontline setting. Since the response rate with lenvatinib is approximately twice that of dabrafenib or vemurafenib with a longer median duration of response and progression-free interval, lenvatinib is most often considered frontline therapy. Furthermore, evidence to support its use stems from a large, randomized, multicenter study. MKIs genomically targeting *BRAF* V600E, on the other hand, have only been studied in small, multicenter trials, and randomized comparative data with lenvatinib are lacking. Clinicians may elect to treat with a specific inhibitor of *BRAF* V600E, in particular when the use of an antiangiogenic agent poses more risk for bleeding, including tumors invading blood vessels or uncontrolled hypertension. It is worth mentioning that there is a

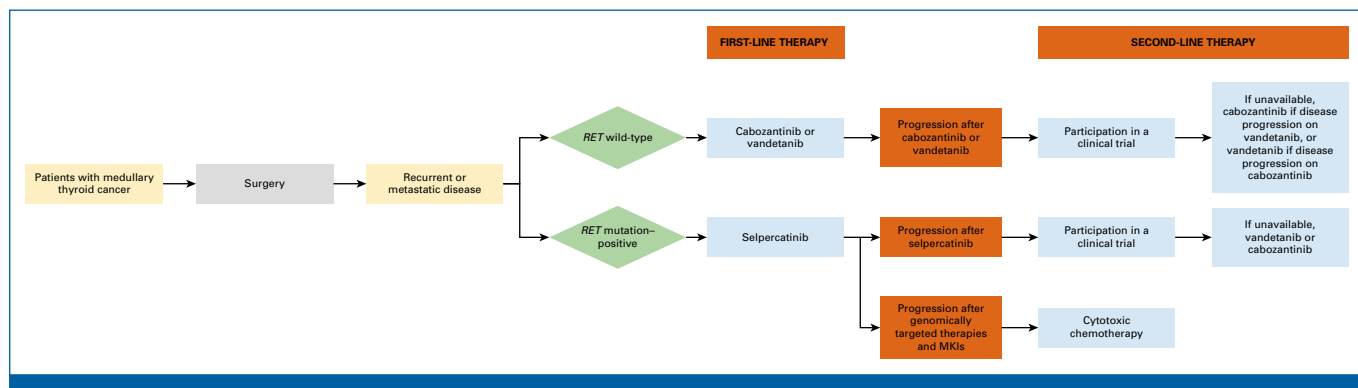


FIG 4. Systemic therapy of medullary thyroid cancer algorithm. MKI, multikinase inhibitor.

forthcoming publication of a large international RCT of dabrafenib and trametinib (presented in abstract form), which demonstrated a PFS benefit (12.8 months for dabrafenib and trametinib v 3.7 months for placebo) with a HR of 0.38 (95% CI, 0.25 to 0.57).⁷⁷ This study may provide additional evidence to support the use of dabrafenib-containing regimens, although it does not provide comparative data versus lenvatinib.

Recommendation 2.2

Literature review and analysis. In a phase II, multicenter study, patients with *BRAF* V600E mutation-positive, RAI-refractory thyroid cancers were randomly assigned to dabrafenib (n = 26) alone versus dabrafenib plus trametinib (n = 27). Approximately 20% of patients on each arm were treated with MKI prior to enrollment. The ORR by RECIST 1.1 was 42% (95% CI, 23% to 63%) for dabrafenib and 48% (95% CI, 29% to 68%) for dabrafenib plus trametinib (*P* = .67). With a median follow-up time of 23 months, the median objective response was 18.3 months (95% CI, 5.0 to NE) for dabrafenib and 17 months for the combination arm (95% CI, 9.7 to 44.5); the PFS was 10.7 months (95% CI, 3.8 to 34.7) for dabrafenib alone and 15.1 months (95% CI, 12.3 to 37.3) for combination therapy. Skin reactions, fatigue, fevers, and hyperglycemia were the most common toxicities reported with single-agent therapy or the combination.⁸

Treatment with vemurafenib following upfront TKI therapy demonstrated a partial response rate of 27.3% (95% CI, 10.7 to 50.2), and 27.3% achieved stable disease for at least 6 months with a disease control rate of 55% (95% CI, 32 to 76). With a median follow-up of 12.0 months, the median PFS was 8.9 months (95% CI, 5.5 to NE) and the median OS was 14.4 months (95% CI, 8.2 to 9.5).¹⁰

For tumors harboring *RET* gene fusions, a phase I/II trial with selpercatinib reported an ORR of 79% (95% CI, 54 to 94).²⁶ Patients who were previously treated experienced durable responses. At 1 year, 71% of responses were ongoing, and 64% of patients were progression-free. In the phase II trial with pralsetinib, patients who were previously treated with an MKI achieved an ORR of 90.9% (95% CI, 70.8 to 98.9) with a median PFS of 25.4 months.

For tumors with *NTRK* gene fusions, in a pooled analysis of phase I/II trials, larotrectinib produced an 86% ORR (95% CI, 64 to 97).⁷⁴ The median response time was 1.9 months, and the median duration of response was between 35 and 43 months for patients with RAI-refractory, differentiated thyroid cancer. The median PFS ranged from 39 to 44 months, and the 6-year OS rate was 71% (95% CI, 50 to 91). Similarly, entrectinib also demonstrated substantial activity in thyroid cancer with an overall response rate of 63% (95% CI, 38 to 84). In a pooled analysis of phase I/II trials, the median time to response was 1.8 months and the median duration of response 10–20 months, with a median PFS of 13.8 months.

Clinical interpretation. Patients whose thyroid cancers have actionable genomic alterations (*RET*, *NTRK*, and *BRAF* V600E) and whose disease has progressed on treatment with MKI therapies (lenvatinib or sorafenib) should be treated with *RET*, *NTRK*, *BRAF*, or *MEK* inhibitors, accordingly. Except for *BRAF* or *MEK* inhibitors, which produce modest response rates with more limited disease control, *NTRK* and *RET* inhibitors provide high response rates and durable disease control when used as second-line therapy. Generally, these agents have manageable toxicity profiles.

Question 3

In patients with RAI-refractory, well-differentiated thyroid cancer (papillary, follicular, oncocytic), does immunotherapy compared to targeted agents or MKIs impact response and/or survival and what should be recommended in the first-line and subsequent-line setting?

Recommendation 3.1

Literature review and analysis. A phase II non-randomized clinical trial evaluating dual immune checkpoint inhibition with nivolumab (3 mg/kg once every 2 weeks) and ipilimumab (1 mg/kg once every 6 weeks) in 49 patients with radioiodine refractory differentiated thyroid cancer demonstrated a low ORR of 9.4% (3/32 [95% CI, 2.8% to 28.5%]) in the differentiated thyroid cancer cohort.⁵ Responses were primarily observed in patients with oncocytic (2/6 [33.0%]) and poorly differentiated subtypes (1/5 [20.0%]). Similarly, the phase II KEYNOTE-158 study with single-agent pembrolizumab in 103 patients with histologically and/or cytologically confirmed papillary or follicular thyroid carcinoma demonstrated modest antitumor activity with response rates of 6.8% (95% CI, 2.8% to 13.5%), regardless of PD-L1 expression.⁷⁸

Clinical interpretation. These studies did not meet their primary end points. As such, the routine use of immunotherapy in well-differentiated thyroid cancer is not recommended, although a minor subset of patients may derive benefit within a clinical trial setting.

Recommendation 3.2

Literature review and analysis. There are very limited data to support the addition of immunotherapy to MKI therapy in patients with RAI-refractory, differentiated thyroid cancers. In a small, multicenter study conducted by the International Thyroid Oncology Group, the primary end point of overall response was met in a cohort of 25 patients who were treated with pembrolizumab upon disease progression with lenvatinib. Sixteen percent (n = 4) experienced partial responses, and the median PFS was 10.0 months (95% CI, 7.0 to 17.9).⁷⁹ Additionally, this study did include a first-line cohort of lenvatinib and pembrolizumab combined, but results were similar to lenvatinib alone (supporting the

current recommendation that first-line pembrolizumab is not recommended).

Clinical interpretation. Combining lenvatinib with pembrolizumab may enhance immune activation and anti-tumor effects, whereby MKIs may modulate the tumor microenvironment to improve response to immune checkpoint blockade. However, durable tumor regression in low-mutation-burden tumors such as differentiated thyroid cancers is not established. Second-line therapies for such patients are relatively limited and are toxic, especially when initiating treatment at the approved starting dosage of an MKI. Thus, pembrolizumab may be added to treatment in patients who have disease progression on a dosage of lenvatinib that was previously sustaining a disease response and whose MKI-related side effects were well managed.

Question 4

In patients with RAI-refractory, well-differentiated thyroid cancer (papillary, follicular, oncocyctic), cytotoxic chemotherapy compared to targeted agents or MKIs impact response and/or survival in the first-line and subsequent-line setting?

Recommendation 4.1

Literature review and analysis. Doxorubicin, either as a single agent or in combination with cisplatin, has been associated with only modest responses in the treatment of RAI-refractory, differentiated thyroid cancers. Specifically, one randomized trial of doxorubicin (n = 41) versus combination doxorubicin and cisplatin (n = 43) demonstrated a 17% (n = 7) response rate for monotherapy and 26% (n = 6) for the combination.⁸⁰

Clinical interpretation. Cytotoxic chemotherapy has a limited role in the management of RAI-refractory, well-differentiated thyroid cancer. Doxorubicin, the only US Food and Drug Administration (FDA)-approved cytotoxic therapy, should only be considered in patients with metastatic, rapidly progressive, symptomatic, or imminently threatening disease that is not amenable to control by other treatment modalities, including surgery, radiation, MKIs, or genomically targeted therapy. The use of cytotoxic therapy as frontline therapy is not recommended outside the context of clinical trials.

Recommendation 4.2

Literature review and analysis. There is scarcity of data in support of cytotoxic chemotherapy in this population. There are randomized data that demonstrated modest response rates (approximately 20%-25%) as cited previously, but there is limited evidence regarding the use of these medications in the context of targeted therapies.

Clinical interpretation. Cytotoxic chemotherapy should only be for patients with metastatic, rapidly progressive,

symptomatic, or imminently threatening disease not otherwise amenable to control through other approaches, including kinase inhibitors, preferably within the context of a therapeutic clinical trial. Doxorubicin is the only cytotoxic approved agent for thyroid cancer. Its activity in the treatment of RAI-refractory, differentiated thyroid cancer, however, is very modest with infrequent, short-lived responses. Furthermore, combination regimens with doxorubicin and cisplatin have been explored without clear benefit over single-agent doxorubicin with increased toxicity.

DIFFERENTIATED HIGH-GRADE OR POORLY DIFFERENTIATED

Prior to 2022, the term PDTC was used to describe follicular cell neoplasms exhibiting limited follicular differentiation and intermediate behavior between differentiated and undifferentiated (anaplastic) thyroid carcinoma. Various diagnostic criteria, such as the Turin proposal and Hiltzik's histologic grade, defined PDTC based on pathological features including absence of papillary thyroid carcinoma (PTC)-like nuclei, mitotic index, growth pattern, and tumor necrosis.

The WHO fifth edition Classification of Endocrine and Neuroendocrine Tumors introduced a new diagnostic category called DHGTC.⁸¹ This category includes papillary, follicular, and oncocyctic thyroid carcinomas with high-grade features (tumor necrosis, mitotic index) and a prognosis similar to that of PDTC. Consequently, the broader group termed high-grade follicular cell-derived nonanaplastic thyroid carcinoma now encompasses both PDTC (commonly RAS mutation-positive and lacks conventional PTC nuclear features) and DHGTC (PTCs in this group are commonly BRAF V600E mutation-positive and show diagnostic nuclear features).

The following recommendations are largely derived from small subgroups of PDTC or DHGTC that were included in larger studies of well-differentiated and ATC. To be included in evidence tables for the PDTC or DHGTC sections, studies were required to explicitly state the inclusion of at least 10 patients with PDTC. Although these studies generally did not report outcomes specifically for the PDTC subgroup, overall conclusions from the study (eg, benefit of MKI over placebo) were thought to be generalizable to PDTC.

There is lack of standardization and significant heterogeneity in the definitions of PDTC included in these trials, most of which were conducted prior to the WHO fifth edition classification.

Question 5

In patients with RAI-refractory DHGTC or PDTC, do MKIs compared to placebo or observation impact survival and

what should be recommended in the first-line and subsequent-line setting?

Recommendation 5.1

Literature review and analysis. Three RCTs that compared MKI to placebo in the first-line RAI-refractory setting for DTC, which also included ≥ 10 patients with explicitly labeled PDTC, were reviewed.⁴⁴⁻⁴⁶ In the phase III SELECT trial, lenvatinib led to a PFS benefit (18.3 v 3.6 months; HR, 0.21) compared to placebo in the overall population; outcomes for the PDTC subgroup (28 patients in the lenvatinib arm, and 19 in the placebo arm) were not reported separately.⁴⁵ In the phase III DECISION trial, sorafenib also led to a PFS benefit (modified PFS [mPFS] 10.8 v 5.8 months; HR, 0.59) compared to placebo in the overall population; again, results in the PDTC subgroup (24 patients in the sorafenib arm, 16 in placebo) were not reported separately.⁴⁴ Finally, in a randomized phase II trial comparing vandetanib to placebo, the overall population had a PFS benefit (HR, 0.63; mPFS 11.1 v 5.9 months); the subgroup including follicular (n = 20) and PDTC (n = 57) had a PFS HR of 0.83 favoring vandetanib.⁴⁶ Notably, a subsequent randomized phase III trial comparing vandetanib to placebo did not show a significant PFS benefit⁸²; this study was not formally included because the number of patients with PDTC was not explicitly stated.

Several other studies including retrospective studies and prospective clinical trials for both DTC and ATC were reviewed, but either did not report the number of patients with PDTC or included fewer than 10 patients with PDTC.^{5,37,79,83,84} In particular, the ATLEP study of lenvatinib and pembrolizumab included 27 patients with ATC and eight patients with PDTC, in whom 6/8 (75%) achieved partial response and 2/8 (25%) achieved stable disease⁸⁵; however, the full results of this study have not been published to date. A more recent study of lenvatinib with pembrolizumab also showed promising outcomes (mPFS 26.8 months in MKI-naïve patients and 10.0 months in patients who have disease progression on lenvatinib), but also included only eight patients with PDTC and did not meet criteria for inclusion.⁷⁹

Clinical interpretation. The results of the prospective randomized trials confirm that MKI leads to improved PFS compared to placebo for first-line RAI-refractory DTC, and likely also provide benefit in patients with PDTC or DHGTC. In particular, lenvatinib has a moderate quality of evidence supporting its use, given more impressive PFS benefit compared to sorafenib or vandetanib.

Thus, for patients with driver mutation–negative PDTC or DHGTC with RAI-refractory and progressive disease requiring systemic therapy, lenvatinib or sorafenib may be considered. Lenvatinib with pembrolizumab may be considered for patients with aggressive PDTC or DHGTC, but

there is insufficient evidence to formally recommend this strategy.

Recommendation 5.2

Literature review and analysis. The literature review did not yield any prospective or retrospective studies of MKI in the subsequent-line setting specifically for PDTC or DHGTC. COSMIC-311,⁷³ which established cabozantinib as second-line therapy, RAI-refractory, differentiated thyroid cancer, included fewer than 10 patients with PDTC and thus did not meet criteria for inclusion as part of the evidence base for this guideline.

Clinical interpretation. The COSMIC-311 trial demonstrated that cabozantinib significantly improved PFS in patients with previously treated RAI-refractory, differentiated thyroid cancer. However, due to the lack of dedicated trials in the PDTC population, there is currently insufficient evidence to formally recommend cabozantinib as a standard second-line treatment.

Question 6

In patients with RAI-refractory DHGTC or PDTC, do genomically targeted therapies compared to placebo or observation impact survival in the first-line and subsequent-line setting?

Recommendation 6.1

Literature review and analysis. The literature review did not yield any prospective or retrospective studies of genomically targeted therapies in the first-line or subsequent-line setting specifically for PDTC or DHGTC. While PDTC has a lower rate of actionable genomic alterations, DHGTCs may harbor *BRAF* V600E, *NTRK*, or *RET* alterations. None of the prospective clinical trials of targeted therapies (dabrafenib or trametinib for *BRAF* V600E, seliprecatinib for *RET*, larotrectinib or entrectinib for *NTRK*) included 10 or more patients with explicitly labeled PDTC. Please refer to the differentiated thyroid cancer section for guidelines on targeted therapies for driver mutation–positive differentiated thyroid cancer.

Clinical interpretation. For patients with DHGTC or PDTC that harbor an actionable genomic alteration, targeted therapies extrapolated from the differentiated thyroid cancer section may be considered; however, there is insufficient evidence to formally recommend this.

Question 7

In patients with RAI-refractory DHGTC or PDTC, does immunotherapy compared to targeted agents or MKIs impact response and/or survival in the first-line and subsequent-line setting?

Recommendation 7.1

Literature review and analysis. The literature review did not yield any prospective or retrospective studies of immunotherapy in the first-line or subsequent-line setting specifically for PDTC or DHGTC. A prospective study of ipilimumab and nivolumab for aggressive thyroid carcinoma⁵ as well as the previously mentioned studies of lenvatinib and pembrolizumab^{79,85} all included <10 patients with PDTC and did not report analysis within this patient subgroup.

Clinical interpretation. The combination of lenvatinib with pembrolizumab and the use of ipilimumab or nivolumab are emerging therapeutic strategies that may be considered for patients with PDTC. This is primarily based on extrapolation of data from studies conducted in the broader, patient population with RAI-refractory, differentiated thyroid cancer. The underlying biological hypothesis is that PDTC or DHGTC, which shares characteristics of aggressive differentiated thyroid cancer, might benefit similarly from these systemic approaches. However, while these combinations represent plausible therapeutic avenues, the current evidence base only supports their conditional consideration as treatment options, and there is insufficient evidence to issue a formal recommendation for their routine use in clinical practice.

Question 8

In patients with RAI-refractory DHGTC or PDTC, does cytotoxic chemotherapy compared to targeted agents or MKIs impact response and/or survival and what should be recommended in the first-line and subsequent-line setting?

Recommendation 8.1

Literature review and analysis. The literature review did not yield any prospective or retrospective studies of cytotoxic chemotherapy in the first-line or subsequent-line setting specifically for PDTC or DHGTC. Historical studies of cytotoxic chemotherapy either did not specify the number of or had fewer than 10 patients with PDTC. A more recent study of salvage pemetrexed-carboplatin in patients with refractory advanced thyroid cancer included seven patients with differentiated thyroid cancer or PDTC.⁴⁹

Clinical interpretation. There is insufficient evidence to recommend cytotoxic chemotherapy for PDTC or DHGTC; however, regimens such as carboplatin or pemetrexed, taxanes, or doxorubicin may be considered in cases after disease progression on alternate systemic therapies.

ANAPLASTIC (ATC)

ATC requires a multidisciplinary approach to therapy including surgery, radiation, systemic therapy, and airway management. The workup should be swift and include stabilization of the airway, determination of the *BRAF*

V600E status, stage, and resectability. In general, patients with stage IVA and IVB cancers without a *BRAF* V600E mutation should undergo surgery when feasible and then complete radiation to the neck with radiosensitizing chemotherapy. Patients with stage IVB with *BRAF* V600E mutation should be offered upfront neoadjuvant therapy, followed by surgery when possible, and radiation with radiosensitizing chemotherapy. Patients with stage IVC *BRAF* V600E mutations should be considered for *BRAF*-directed systemic therapy. These cases are more complex, and their treatment requires consideration of palliative radiation to the neck versus upfront systemic therapy when the airway is stable.

The following recommendations pertain to the use of systemic therapy within this context.

Question 9

In patients with ATC, do MKIs compared to placebo or observation impact survival and what is recommended in the first-line setting and subsequent-line setting?

Recommendation 9.1

Literature review and analysis. Three prospective studies have evaluated the efficacy of single-agent lenvatinib.^{62,63,66} The largest study reported a 1-year survival rate of 11.9% among 42 patients with ATC.⁶³ Furthermore, prospective evaluations of patients with ATC without a genomic mutation treated with checkpoint inhibition demonstrate similarly poor median OS of 6.2 months.⁶⁶ A prospective, single-arm, phase II clinical trial investigated the combination of lenvatinib and pembrolizumab in 25 patients with ATC⁶¹ without a *BRAF* V600 mutation; 96% of patients received either surgery or radiation to the primary tumor prior to study entry. The primary end point was median OS by at least 3 months compared to the historical benchmark of 3-month median OS observed with single-agent lenvatinib from a prior phase II clinical trial.⁶² The study met its primary end point with median OS in the combination trial of 11.4 months (95% CI, 7.8 to 35.6; *P* < .025). The best overall response in target lesions was 36%. Serious adverse events, specifically bleeding and fistula formation, were rare but occurred, warranting caution when considering this regimen in patients at risk for these complications.

Clinical interpretation. Despite being based on a single-arm, nonrandomized study, the magnitude of survival benefit compared to historical outcomes supports the use of lenvatinib plus pembrolizumab as a preferred systemic option for patients with metastatic, nongenomically altered ATC. Given the high mortality rate of ATC, the improved survival and acceptable response rate (36%) justify this approach, while acknowledging the need for careful toxicity monitoring, particularly concerning bleeding and fistula formation.

Recommendation 9.2

Literature review and analysis. There is no published literature identified evaluating second-line therapy after disease progression on lenvatinib or lenvatinib plus pembrolizumab for ATC without a genomic mutation.

Clinical interpretation. The absence of dedicated literature regarding second-line treatment options after disease progression on lenvatinib or lenvatinib plus pembrolizumab for ATC without a genomic mutation creates a significant therapeutic challenge. Disease usually progresses quickly after first-line therapy; clinicians must carefully weigh the marginal benefit of further systemic therapy against the potential for treatment-related toxicity and make best supportive care a critical component of the discussion. Palliation of symptoms of uncontrolled cancer should be prioritized. Patients are recommended to participate in a clinical trial.

Question 10

In patients with ATC, do genomically targeted therapies compared to placebo or observation impact survival and what should be recommended in the first-line and subsequent-line setting?

Recommendation 10.1

Literature review and analysis. Seven studies with BRAF V600E-directed targeted therapy alone or in combination with anti-PD-1 or PD-L1 immunotherapy were included. No randomized trials were found. All trials were single-arm prospective⁵²⁻⁵⁴ or retrospective series.⁵⁶⁻⁵⁹ The largest of the prospective trials with targeted therapy alone (dabrafenib and trametinib) included 36 patients, while the largest retrospective series with combination BRAF V600E-targeted therapy plus immune checkpoint inhibitor therapy versus BRAF V600E-targeted therapy alone included 71 patients.⁵⁴ Median PFS and OS were 6.7 and 14.5 months, respectively, and the response rate was 58% in patients with confirmed BRAF V600E mutation. In the retrospective trial, there were 23 patients treated with BRAF V600E-directed therapy alone, and the median OS was 9 months. The patients in this study never received immune checkpoint inhibitor therapy nor surgical resection after starting dabrafenib and trametinib. Similarly, the other retrospective trials showed a median OS of 6.9 to 10.7 months.^{56,57} A retrospective study looking at surgery in patients who were treated with dabrafenib and trametinib ± checkpoint inhibitor therapy indicates that patients with BRAF V600E mutation-positive ATC who are treated with upfront neoadjuvant dabrafenib and trametinib ± immune checkpoint inhibitor followed by surgery have the longest survival when compared to those who had upfront surgery or no surgery.⁵⁸ There are inherent biases of such a study due to the retrospective nature. A prospective study with neoadjuvant

dabrafenib, trametinib, and pembrolizumab has been completed but is not yet published (ClinicalTrials.gov identifier: [NCT04675710](https://clinicaltrials.gov/ct2/show/study/NCT04675710)).

Clinical interpretation. These results support the use of BRAF V600E-targeted therapy in patients with BRAF V600E mutation-positive ATC. However, the true median OS results of the prospective trial of dabrafenib and trametinib alone should be interpreted with caution. Since patients who responded were able to proceed to surgical resection or radiation, the reported median OS might overestimate the true survival benefit attributable to the drugs alone, as the cure or control achieved by subsequent local therapy likely contributed significantly to the extended survival. Given this context, the use of these drugs as neoadjuvant therapy followed by surgery or radiotherapy may be the most impactful.

Recommendation 10.1.1

Literature review and analysis. The only trial to compare patients treated with BRAF/MEK inhibitor (dabrafenib + trametinib) to BRAF/MEK inhibitor + immune checkpoint inhibitor (dabrafenib + trametinib + pembrolizumab) was a nonrandomized, retrospective study.⁵⁹ The primary analysis included 71 patients; 34 treated with dabrafenib + trametinib + pembrolizumab and 14 also received pembrolizumab in addition to dabrafenib + trametinib at disease progression (total n = 48). There were 23 patients in the dabrafenib + trametinib alone group. The median OS of patients in the upfront dabrafenib + trametinib + pembrolizumab or the addition of pembrolizumab to dabrafenib + trametinib at disease progression was 17 months, and 9 months in the dabrafenib + trametinib alone group. An exploratory group of an additional 23 patients who underwent surgery after upfront dabrafenib + trametinib + pembrolizumab had a median OS of 63 months. A prospective, nonrandomized trial included 19 patients treated with BRAF or MEK inhibitor + anti-PD-L1 drugs.⁵¹ The median PFS and OS were 13.9 and 43 months, respectively. Patients were permitted to undergo surgery during the trial. Both trials included patients with stage IVB and IVC diseases. It should be noted that patients who underwent surgical resection after BRAF or MEK inhibitor + immune checkpoint inhibitor therapy resumed these drugs shortly after surgery. Patients with stage IVB disease typically underwent chemoradiation after surgical resection and then continued BRAF or MEK inhibitor + immune checkpoint inhibitor therapy.

Clinical interpretation. Patients with stage IVB and IVC BRAF V600E mutation-positive ATC should be considered for upfront dabrafenib and trametinib + pembrolizumab to rapidly control the disease, reduce tumor bulk, and, crucially, convert initially unresectable or borderline-resectable disease into a surgically resectable state. After a favorable response, surgical resection may be considered with a multidisciplinary team to assess the extent of response and surgical feasibility.

Recommendation 10.2

Literature review and analysis. Larotrectinib and entrectinib are both FDA-approved for treating solid tumors with *NTRK* fusions in both adult and pediatric patients. In the seven patients with ATC from a pooled analysis of three single-arm trials with larotrectinib, the ORR was 29% (95% CI, 4 to 71), with two partial responses, with 50% maintaining the response at 12 months.⁷⁴ One additional patient had stable disease, and both the 12- and 24-month PFS was 17%, with an OS at those time points of 50% and 17%, respectively. Four out of seven patients had not received prior systemic therapy, and three had received one line of prior therapy, which was with chemotherapy. In a retrospective study of 65 patients with *NTRK* fusion-positive thyroid cancer, two of four patients with ATC had a partial response to therapy.⁸⁶

Selpercatinib is FDA approved for *RET* fusion-positive thyroid cancer and *RET* mutation-positive MTC. Two patients with ATC were included in the Libretto-001 prospective study, with one patient reported having a partial response that lasted for 18 months.²⁶

Clinical interpretation. Given the extremely poor prognosis of ATC and limited prospective data, the existing FDA approvals for these agents in tumors harboring the respective fusions the substantial and durable response rates observed with *NTRK* inhibitors (eg, larotrectinib, entrectinib) and *RET* inhibitors (eg, selpercatinib, pralsetinib) in other advanced thyroid and solid tumors provide strong justification for their use in this setting while awaiting more extensive ATC-specific clinical trial data.

Recommendation 10.3

Literature review and analysis. There is no published literature evaluating subsequent-line therapy after disease progression on genomically targeted therapy. Given the poor outcomes of these patients, participation in clinical trials is recommended. However, prospective evaluation demonstrates a low response rate in ATC without a genomic mutation managed with lenvatinib alone or lenvatinib with pembrolizumab, and may be offered as an established, broad-spectrum, second-line systemic option when specific targeted salvage therapies or clinical trials are unavailable.

Clinical interpretation. Clinical trials, when available or feasible, should be considered in patients who have disease progression on genomically targeted therapy. If these are not available [NA], lenvatinib ± pembrolizumab may be considered.

Question 11

In patients with ATC, does immunotherapy impact response and/or survival and what should be recommended in the first-line and subsequent-line setting?

Recommendation 11.1

Literature review and analysis. There are two studies showing efficacy of the combination therapies, lenvatinib + pembrolizumab or ipilimumab + nivolumab, for treatment of advanced ATC without a genomic mutation in first-line setting. One prospective, single-arm, phase II clinical trial using lenvatinib in combination with pembrolizumab in non-*BRAF* V600E mutation-positive ATC with 25 patients were studied, of which 96% had upfront treatment to the primary tumor prior to study entry. The primary end point was median OS compared to 3-month OS from the single-agent lenvatinib clinical trial with the goal of improving survival by 3 months.⁶² The median OS in the combination trial was 11.4 months, thus meeting the study end point (95% CI, 7.8 to 35.6; $P < .025$). The best overall response in target lesions was 36%. Bleeding and fistula were rare but serious events that merit caution in patients at risk for these complications. Another study with ipilimumab + nivolumab⁵ included differentiated thyroid cancers, including MTC and ATC. This was a phase II nonrandomized trial of intravenous nivolumab (3 mg/kg) once every 2 weeks and ipilimumab (1 mg/kg) once every 6 weeks. Treatment was continued until disease progression or intolerable side effects, or maximum time of 2 years. 10 patients with ATC were included in this study. 90% of patients had prior surgery for thyroid cancer, 80% had prior radiation therapy, and 70% had received prior systemic therapy. Eight patients discontinued treatment because of disease progression ($n = 4$), adverse effects ($n = 3$), or withdrew consent ($n = 1$). Two patients completed the entire 2 years of treatment. Three of the 10 patients achieved partial response with ORR of 30% (95% CI, 6.7% to 65.2%). The median PFS was 4.3 months (95% CI, 0.5 to NA). The 12- and 24-month OS rates were 55.6% (95% CI, 20.4% to 80.5%). The observed ORR was 30% and 50%, which is favorable in comparison to anti-PD-1 monotherapy.

Clinical interpretation. For patients with advanced ATC without a genomic mutation, treatment selection is challenging due to the limited efficacy of historical options and the aggressive nature of the disease. The combination of lenvatinib + pembrolizumab or the dual immune checkpoint blockade of ipilimumab + nivolumab may be offered as systemic therapeutic options. Despite the availability of these systemic options, ATC carries an extremely high risk of local complications (eg, airway compression, bleeding, dysphagia). Therefore, upfront palliation and control of the primary tumor should be the immediate priority.

Recommendation 11.2

Literature review and analysis. The only trial to examine the addition of pembrolizumab to dabrafenib plus trametinib after disease progression with dabrafenib plus trametinib alone was a retrospective study of 71 patients with *BRAF* mutation-positive ATC. Fourteen patients who had disease progression on dabrafenib plus trametinib alone had

pembrolizumab added to the regimen. The median OS of these patients was 16 months (95% CI, 6.4 to 25.6).⁵⁹

Clinical interpretation. While the retrospective nature and small cohort size of this study limit the strength of the evidence, the observed median OS of 16 months following the addition of pembrolizumab to dabrafenib plus trametinib in patients whose disease progressed on the dual therapy alone suggests a clinically meaningful benefit in the highly aggressive, *BRAF* mutation–positive ATC setting. Pending prospective data, this triplet regimen may be considered as a salvage option for patients who have disease progression on *BRAF* or *MEK* inhibitors.

For patients with stage IVB disease who have completed upfront multimodal treatment (surgery when feasible + radiation with radiosensitizing chemotherapy), adjuvant treatment with pembrolizumab for 2 years may be considered, starting 4–6 weeks after completion of radiation. A cohort study of patients with stage IVB (locoregional disease; *N* = 16) used a pooled analysis of prospective and retrospective patients treated with adjuvant pembrolizumab after upfront surgery (when feasible) and chemoradiation compared to age- and treatment-matched historical controls who did not receive adjuvant pembrolizumab.⁸⁷ The median PFS was not reached in the adjuvant pembrolizumab arm and was 5.4 months in the control arm (95% CI, 2.04 to 16.20; *P* = .006; HR, 0.24 [95% CI, 0.08 to 0.73]). The median OS was not reached in the adjuvant pembrolizumab group and was 31 months in the control arm (95% CI, 13.9 to NA; *P* = .009; HR, 0.11 [95% CI, 0.01 to 0.83]). Immune-related adverse events included grade 2 pneumonitis. One other patient had gastric ischemia leading to sepsis and death, but it was unclear if related to pembrolizumab since the patient was on treatment for chronic lymphocytic leukemia. Thus, patients with stage IVB ATC who complete surgery (when feasible) and definitive radiation ($\pm$ radiosensitizing chemotherapy) may be considered for adjuvant pembrolizumab. However, patients should be made aware of potential immune-related adverse events.

Question 12

In patients with ATC, does cytotoxic chemotherapy compared to targeted agents or MKIs impact response and/or survival and what should be recommended in the first-line and subsequent-line setting?

Recommendation 12.1

Literature review and analysis. No comparative trials of targeted therapy and cytotoxic chemotherapy have been completed in ATC, and studies utilizing cytotoxic chemotherapy in ATC predate the use of targeted therapy. Due to time delay from ordering to receiving molecular testing, in a retrospective trial of 16 patients with ATC, five patients

received “bridging” chemotherapy with weekly nab-paclitaxel or paclitaxel, and one patient received carboplatin and paclitaxel until return of molecular testing and initiation of molecularly focused therapy. Time on bridging therapy was between 1 and 8 weeks, and none of the patients had disease progression while on bridging cytotoxic chemotherapy.⁴⁸

Clinical interpretation. There is no evidence to support the use of cytotoxic chemotherapy in patients who are candidates for genomically targeted therapies or MKIs. However, despite the limited data, in instances where molecular data are not available or there is rapidly progressive disease, clinicians may offer cytotoxic chemotherapy.

Recommendation 12.2

Literature review and analysis. The FACT trial⁴⁷ investigated the role of adding the vascular disrupting agent fosbretabulin to standard chemotherapy (carboplatin and paclitaxel) in 80 patients with advanced thyroid cancer, and reported a nonsignificant difference in response rate, at 20% and 16%, respectively, and no complete responses. Furthermore, there was a nonsignificant difference in OS with fosbretabulin (5.2 v 4 months). However, it is important to note that none of the patients in this trial had received prior targeted therapy.

A small retrospective series examined the use of carboplatin and pemetrexed in 14 patients, including 11 with refractory differentiated thyroid cancer and 3 with ATC. All three patients with ATC had received prior immunotherapy and MKI. One patient, who also harbored a *BRAF* V600E mutation, did respond to carboplatin and pemetrexed that was sustained beyond 13 months.⁴⁹

Clinical interpretation. There are limited data supporting cytotoxic chemotherapy in ATC. Therefore, clinical trial enrollment is favored and strongly encouraged for patients who fail targeted therapy or MKIs. In the absence of clinical trials, cytotoxic chemotherapy can be considered. There is no favored cytotoxic chemotherapeutic agent, and combination chemotherapy has not been proven to be better than single-agent chemotherapy and decisions.

MEDULLARY (MTC)

The primary treatment of MTC is surgery. The following recommendations pertain to recurrent or metastatic disease after primary treatment.

Question 13

In patients with unresectable locally advanced and/or metastatic MTC, do MKIs compared to placebo or observation impact survival and what should be recommended in the first-line setting and subsequent-line setting?

Recommendation 13.1

Literature review and analysis. Three RCTs investigated a MKI compared to placebo in patients with unresectable locally advanced and/or metastatic MTC.^{32–34} ZETA was a phase III trial randomizing 331 patients to vandetanib or placebo in a 2:1 ratio, with a primary objective of PFS.³⁴ Progressive disease was not a requirement for trial entry. At disease progression, patients were unblinded, and those on placebo were offered vandetanib. The predicted median PFS with vandetanib was 30.5 versus 19.3 months with placebo (HR, 0.46; 95% CI, 0.31 to 0.69; $P < .001$). The ORR per RECIST with vandetanib was 45%. Responses were seen in *RET* mutation–positive, –negative, and –unknown patients. OS data were immature at cutoff, but post hoc analysis of 184 ZETA patients with symptomatic and progressive disease at baseline showed no OS difference between the two groups. Adverse events led to treatment discontinuation in 12% of patients on the vandetanib arm. The phase III trial, EXAM, randomly assigned 330 patients with disease progression within the prior 14 months to cabozantinib or placebo in a 2:1 ratio, with a primary objective of PFS.³² Crossover to open-label cabozantinib at disease progression in patients on placebo was not allowed. Median PFS with cabozantinib was 11.2 versus 4.0 months with placebo (HR, 0.28 [95% CI, 0.19 to 0.40]; $P < .001$). A PFS benefit was seen across subgroups, including patients who had received a prior MKI and in *RET* mutation–positive, –negative, and –unknown patients. The ORR with cabozantinib was 28%. Median OS with cabozantinib versus placebo was 26.6 versus 21.1 months, which did not reach statistical significance (stratified HR, 0.85 [95% CI, 0.64 to 1.12]; $P = .24$). Adverse events led to treatment discontinuation in 16% on the cabozantinib arm. Anlotinib was studied in a phase IIB trial randomizing 91 patients with MTC to anlotinib versus placebo in a 2:1 ratio, with a primary objective of PFS.³³ At disease progression, patients were unblinded, and those on placebo were offered anlotinib. Median PFS with anlotinib was 20.7 months versus 11.1 months with placebo (HR, 0.53 [95% CI, 0.30 to 0.95]; $P = .029$). ORR with anlotinib was 48.4%. Follow-up for OS is ongoing. Adverse events led to treatment discontinuation in 16.1% of patients on anlotinib. This drug is approved in China and not available in the United States.

Clinical interpretation. In patients with locally advanced and/or metastatic MTC, three MKIs, namely cabozantinib, vandetanib, and anlotinib (approved in China), demonstrated significantly improved PFS compared to placebo in RCTs. These studies predated the phase III LIBRETTO-531 study discussed subsequently, and enrolled patients regardless of *RET* mutation status.²¹ However, given the superior efficacy and tolerability of selpercatinib in *RET* mutation–positive MTC, as shown in LIBRETTO-531, the recommendation for MKIs in the first-line treatment of patients with MTC is limited to patients with *RET* wild-type disease. There is no head-to-head comparison of MKIs in MTC, and cross-trial comparisons are limited due to

differences in study design and patient populations. Therefore, the choice of first-line MKI should be made on a case-by-case basis.

Recommendation 13.2

Literature review and analysis. Enrollment in the ZETA trial was limited to patients who were treatment-naïve.³⁴ However, real-world analysis of 48 patients with locally advanced and/or distant metastatic MTC who were treated with vandetanib and/or cabozantinib revealed second-line vandetanib following first-line cabozantinib may result in partial responses, as can second-line cabozantinib following first-line vandetanib.⁴² EXAM did allow prior MKI treatment. Twenty-one percent of patients received a prior MKI, including vandetanib and sorafenib, and the prespecified subgroup analysis confirmed a significant PFS benefit in these patients.

Clinical interpretation. In patients with *RET* wild-type recurrent or metastatic MTC who have received prior MKI therapy, the limited available data regarding second-line treatment or beyond suggest that patients can derive clinical benefit from MKI treatment beyond the first-line setting, with the best evidence available supporting vandetanib in patients who had disease progression on cabozantinib or vice versa.^{32,42}

Question 14

In patients with MTC, do genomically targeted therapies compared to placebo or observation impact survival and what is recommended in the first-line setting and subsequent-line setting?

Recommendation 14.1

Literature review and analysis. Two *RET* kinase-specific inhibitors were studied in the phase I/II setting in patients with *RET* mutation–positive locally advanced and/or metastatic MTC, either with or without prior MKI treatment, namely selpercatinib and pralsetinib.^{25,26} Both *RET*-specific therapies demonstrated high ORRs, long median PFS, and a well-tolerated safety profile in patients who were previously treated and treatment-naïve. Selpercatinib was subsequently studied in LIBRETTO-531, a phase III RCT comparing selpercatinib to physician's choice (cabozantinib or vandetanib) in 291 patients with treatment-naïve, *RET* mutation–positive, locally advanced and/or metastatic MTC who had disease progression within 14 months from enrollment.²¹ Patients were allocated 2:1 to selpercatinib versus the control arm, and followed for PFS as the study's primary end point. Crossover to open-label selpercatinib with disease progression in patients on the control arm was allowed. Median PFS with selpercatinib was not reached versus 16.8 months in the control group (HR, 0.28 [95% CI, 0.16 to 0.48]; $P < .001$). Treatment failure–free survival, defined as the time from randomization to disease progression,

discontinuation of treatment due to treatment-related adverse events, or death, was a key secondary end point considered a composite measure of treatment-related efficacy and tolerability, and it was significantly improved with selpercatinib versus control. At a median follow-up of 15 months, a total of 18 deaths had occurred. The observed HR for death from any cause was 0.37 (95% CI, 0.15 to 0.95). Pralsetinib was not studied in the phase III setting, despite the promising phase I/II results.

Clinical interpretation. Selpercatinib is considered the preferred first-line therapy for progressive *RET* mutation-positive unresectable locally advanced and/or metastatic MTC based on safety and efficacy outcomes from LIBRETTO-531. Long-term follow-up data from the phase I/II selpercatinib study, LIBRETTO-001, support this, showing a higher ORR and longer median PFS in patients who were treatment-naïve compared to patients previously treated with an MKI.²⁷ Of note, *RET*-specific inhibitors have demonstrated similar activity and safety profiles in patients with hereditary MTC harboring germline *RET* mutations.²⁸

Recommendation 14.2

Literature review and analysis. Clinical trials investigating new treatment strategies in patients with *RET* mutation-positive MTC with disease progression on a *RET*-specific inhibitor such as selpercatinib or pralsetinib have not yet been conducted. In the largest series of the development of resistance to *RET*-specific inhibitors in *RET* mutation-positive MTC available to date, both on-target *RET* mutations and bypass pathway acquired resistance alterations were found, sometimes polyclonal, on molecular profiling of progressive disease.²⁹ Response to subsequent lines of therapy was not reported.

Clinical interpretation. The mechanisms of acquired resistance to *RET*-specific inhibitor therapy in patients with *RET* mutation-positive MTC are diverse and often polyclonal, with both on-target and bypass pathway resistance emerging. This is a major clinical challenge necessitating the study of new approaches for this patient population.

Question 15

In patients with MTC, does immunotherapy compared to targeted agents or MKIs impact response and/or survival and what is recommended in the first-line and subsequent-line setting?

Recommendation 15.1

Literature review and analysis. Although several registered trials have explored the potential efficacy of immunotherapy in MTC, limited published studies have not convincingly demonstrated efficacy. In a phase II non-randomized trial, the efficacy of dual immune checkpoint inhibition (nivolumab and ipilimumab) was explored in seven patients with MTC. No responses were observed in this

exploratory cohort. Of the seven patients with MTC, two patients had stable disease, with a clinical benefit rate of 28.6%.⁵ An open-label, nonrandomized, single-center phase II trial of pembrolizumab in recurrent or metastatic MTC enrolled patients with recurrent or metastatic MTC in one of two arms: pembrolizumab with or without an immune-stimulating cancer vaccine.⁸⁸ Only two patients from the vaccine group completed the study, and none of the patients enrolled achieved a response.

Clinical interpretation. Considering the unsatisfactory activity of immunotherapy and no head-to-head trials comparing immunotherapy to targeted agents or MKIs, clinicians should not offer immunotherapy in the first-line setting or when other treatment is available in subsequent lines, outside of participation in clinical trials.

Question 16

In patients with MTC, does cytotoxic chemotherapy compared to targeted agents or MKIs impact response and/or survival and what is recommended in the first-line and subsequent-line setting?

Recommendation 16.1

Literature review and analysis. Cytotoxic chemotherapy has been evaluated in small clinical series of patients with MTC from the 1970s through the 1990s, with agents such as doxorubicin, dacarbazine, streptozocin, cyclophosphamide, and 5-fluorouracil. These studies consistently demonstrated the limited efficacy of cytotoxic chemotherapy in patients with progressive or recurrent MTC. Objective responses were low and usually partial, and short-lived. Median PFS was <6 months, complete responses were exceedingly rare, and there was no proven survival benefit.^{89,90} In a single-arm GETC study (N = 20), alternating 5-fluorouracil plus streptozocin with 5-fluorouracil plus dacarbazine produced three partial responses and 11 long-term stabilizations; no PFS or survival advantage was demonstrated.⁸⁹ In a second GETC series (N = 20), alternating doxorubicin plus streptozocin with 5-fluorouracil plus dacarbazine reported three partial responses and 10 stabilizations, without time-to-event efficacy.⁹⁰ These historical outcomes are in stark contrast to the targeted agents. Moreover, cytotoxic regimens are associated with significant toxicities, including myelosuppression, GI intolerance, and cardiotoxicity, which limited their tolerability in most patients.

Clinical interpretation. Due to poor efficacy and high toxicity with cytotoxic chemotherapy, clinicians should not offer cytotoxic chemotherapy in the first-line setting outside of a clinical trial.

Recommendation 16.2

Literature review and analysis. In patients with progressive or recurrent MTC after first-line therapy, conventional cytotoxic chemotherapy shows modest and short-

lived efficacy, with historical series reporting low ORRs and limited disease control despite multiagent regimens alternating 5-fluorouracil plus streptozocin with 5-fluorouracil plus dacarbazine. These data did not demonstrate a reproducible survival advantage and were accompanied by substantial toxicity, which becomes even less acceptable as patients accumulate prior therapies.⁹¹ Current expert guidelines also reflect this, characterizing cytotoxic chemotherapy as having a minor or limited role in metastatic MTC and recommend prioritizing other therapies, reserving cytotoxic chemotherapy for situations where targeted options and clinical trials are exhausted or unsuitable.⁹²

Clinical interpretation. After disease progression on initial therapy, patients derive limited benefit from cytotoxic chemotherapy. The poor efficacy and higher toxicity of cytotoxic chemotherapy in this setting provide a clear clinical rationale to avoid it outside a trial.

LIMITATION OF RESEARCH AND FUTURE RESEARCH

Thyroid cancer comprises a diverse set of diseases with substantial variation in expected outcomes and optimal treatments. In the last decades, paradigm shifts in the diagnosis and characterization of thyroid cancers, including changes in the WHO classification and increasing importance of molecular descriptions, have further impacted the optimal therapies for patients affected by these malignancies. The recommendations included are based on analysis of existing literature and clinical trials, which are affected by these changes as well as the rarity of some of these diagnoses (such as ATC). In each case, the recommendations have been informed by the best available data. For well-differentiated and medullary cancers, there are several studies to reference for treatment recommendations. For differentiated high-grade or PDTC and anaplastic cancers, many recommendations are based on extrapolation due to the type of data available in these diseases.

Regarding differentiated high-grade or PDTC tumors, this characterization was noted in the WHO 2022 update to pathology of thyroid malignancies. As such, it has not been robustly integrated into prior trials. There are several trials of well-differentiated thyroid carcinomas that include this subtype (or its pathological predecessors) and as well several studies of anaplastic thyroid carcinomas that include this subtype (or its pathological predecessors). In these cases, the numbers are limited. Therefore, the overall recommendations are limited, with note of potential acceptable approaches to systemic therapy based on extrapolation.

Similarly, for anaplastic thyroid carcinomas, there have been profound changes in the approach to these malignancies due to newer molecular characterization and integration of systemic therapy into the multidisciplinary evaluation of these patients. However, due to the rarity of the cancer and its propensity to progress rapidly, randomized trials are limited and the numbers of patients included on trials are also small. The recommendations represent the synthesis of

several studies; however, many are based on smaller patient populations, given the disease itself.

Overall, the advances in the treatment of thyroid carcinomas (of all types) have led to improvements over prior approaches, especially with the integration of systemic therapy into multidisciplinary evaluation. There is a significant opportunity to augment the quality of data available and, more importantly, provide patients with novel therapeutic approaches through clinical trials.

PATIENT AND CLINICIAN COMMUNICATION

Clinician and patient communication is extremely important, because of the multiple clinical issues that will likely occur over time. A well-organized, cohesive interprofessional practice approach brings additional, strategic value to this dynamic as well. Patients will typically interact with a variety of clinical personnel over many years. The oncology team should orient patients and their caregivers regarding achieving consistent care and set expectations for long-term follow-up. Care should be given to not overwhelm the patient and caregiver and, if necessary, short-term goals (ie, first follow up) can be prioritized over the “big picture” if necessary. Patients should be offered every available resource for short- and long-term support and encouraged to explore independent support services (ThyCa, etc) if desired. Keeping engaged in an active follow-up plan can keep patients aware of any advances in treatment paradigms and the optimal outcome if their disease recurs through timely intervention.

Additionally, patients often experience distress about the “right questions” to ask their health care team. In practice, it may be of comfort to mention that physicians and providers are generally expected to proactively educate patients with all relevant information regardless of whether or not they are specifically asked by patients. However, patients should feel empowered to ask any and all questions that are meaningful to them.

Patient and clinician communication is a dynamic relationship that evolves over time and benefits from clear communication and trust on both sides. This goal of an effective working relationship may be best achieved by empowering both clinicians and patients to work together to advocate for the best outcome for the patient in ways outlined in this section. See the Discussion Points Between Patients and Clinicians box.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: ASCO Guideline Update.⁹³

PATIENT ACCESS CONSIDERATIONS

Not all patients have consistent access to the resources needed to benefit from ASCO’s expert recommendations on

DISCUSSION POINTS BETWEEN PATIENTS AND CLINICIANS

- What stage is my cancer? Is my cancer curable or just treatable?
- What is the goal of this treatment? Is it curative or palliative?
- What is the success rate of the proposed treatment?
- What side effects should I expect?
- Are there any alternative treatments or observation that may be an option?
- What would you do in my position and why?
- What is the follow-up plan after treatment and what are the benchmarks of success that I should look for (ie, imaging or laboratory studies)?

best practices for prevention, screening, palliative and supportive care, and disease management of cancer.

In the United States, many patients remain unable to reap the benefits of innovative prevention and early detection programs, biomarker testing, and new cancer therapies due to challenges including lack of transportation, stable housing, adequate insurance coverage, food insecurity, health literacy, proximity to a dedicated cancer center, and cost of treatment and other services.⁹⁴ Additionally, some populations experience stigma along with barriers to cancer screening, prevention, and treatment that contribute to these cancer disparities.⁹⁵

Further, geographic disparities can also impact the quality-of-care patients receive. Rural patients are more likely to have worse survivorship outcomes and experience higher mortality rates compared to nonrural patients. This can be attributed, in part, to a lower density of specialists and dedicated cancer centers, as only 21% of nonmetropolitan counties in the United States have one or more practicing oncologists.⁹⁶

In 2025, ASCO updated its guideline protocol template to include a patient access considerations section, allowing the Panel to consider patient access issues prior to starting the literature search.

Patients of all ages, socioeconomic statuses, education levels, and locations may be affected by thyroid carcinoma. At all stages, access to knowledgeable multidisciplinary professionals that understand the importance of coordinated care is crucial to outcomes. This is especially true for recurrent diseases, metastatic disease, and rare cancer entities (such as anaplastic thyroid carcinoma).

Not all patients have consistent access to the resources needed to benefit from ASCO's expert recommendations on

the treatment of thyroid cancer; access to diagnostic testing and multidisciplinary treatment (including surgery, nuclear medicine, radiation oncology, endocrinology, and medical oncology teams) is not consistent throughout the nation, especially in areas that are underserved.

For thyroid carcinoma, pathologic interpretation and molecular testing are necessary to characterize the disease and optimize the treatment plan. Furthermore, access to the necessary systemic therapy medications, including MKIs, may vary based on treatment location. Finally, many thyroid malignancies are rare; expertise in management is not universal and may impact care.

Overall, there is significant opportunity to improve access to swift diagnosis, high-quality pathological diagnosis, and expertise in multidisciplinary treatment of thyroid carcinomas to improve patient care.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients in order to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to consider the complexity and uncertainty created by the presence of MCC and highlight the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles

and coinsurance.^{97,98} Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.^{99,100}

Discussion of cost can be an important part of shared decision making.¹⁰¹ Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.¹⁰¹

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.¹⁰¹

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effectiveness analyses that lack contemporary cost data; agents that are not currently available in either the United States or Canada; or are industry-sponsored. Four cost-effectiveness analyses were identified to inform the topic.¹⁰²⁻¹⁰⁵ The publication dates of these evaluations ranged from 2013 to 2019. While earlier evaluations¹⁰² highlighted a foundational lack of economic data in RAI-refractory, differentiated thyroid cancer, subsequent modeling has yielded inconsistent results regarding the incremental cost-effectiveness ratio for agents like lenvatinib and sorafenib. Specifically, a 2017 analysis found lenvatinib to be cost-effective within a US context,¹⁰³ yet a comprehensive UK evaluation¹⁰⁴ published in 2020 determined that neither lenvatinib nor sorafenib met the acceptable willingness-to-Pay (WTP) threshold for the UK National Health Service; similar issues of ICERs exceeding acceptable thresholds were identified for targeted agents, cabozantinib and vandetanib, in MTC.¹⁰⁵

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a community oncologist member on the panel. The additional role of this community oncologist member on the guideline panel is not only to assess the suitability of the recommendations for implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face

RELATED ASCO GUIDELINES

- Palliative Care for Patients With Cancer¹⁰⁶ (<https://ascopubs.org/doi/10.1200/JCO.24.00542>)
- Patient-Clinician Communication⁹³ (<https://ascopubs.org/doi/10.1200/JCO-26-00118>)
- Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx¹⁰⁷ (<http://ascopubs.org/doi/10.1200/JCO.18.01921>)
- Diagnosis and Management of Squamous Cell Carcinoma of Unknown Primary in the Head and Neck¹⁰⁸ (<http://ascopubs.org/doi/10.1200/JCO.20.00275>)
- Chemotherapy in Combination with Radiotherapy for Definitive-intent Treatment of Stage II to IVA Nasopharyngeal Carcinoma¹⁰⁹ (<http://ascopubs.org/doi/10.1200/JCO.20.03237>)
- Management of Salivary Gland Malignancy¹¹⁰ (<http://ascopubs.org/doi/10.1200/JCO.21.00449>)

of limited resources. The guideline recommendations table and accompanying tools (available at <https://ascopubs.org/topics/asco-guidelines/head-neck-cancer>) were designed to facilitate implementation of recommendations. This guideline will be distributed widely. ASCO guidelines are posted on the ASCO website and are most often published in the *Journal of Clinical Oncology*.

ADDITIONAL RESOURCES

For current information, including selected updates, supplements, and clinical tools and resources, visit <https://ascopubs.org/topics/asco-guidelines/head-neck-cancer>. The Data Supplement for this guideline includes the PRISMA diagram and evidence tables. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the [Apple App Store](#) and [Google Play Store](#)). Listen to key recommendations and insights from panel members on the [ASCO Guidelines podcast](#). The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.org.

ASCO welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of all patients. ASCO guidelines are intended to apply to, and be discussed clearly and compassionately with, all patients. For this

reason, guideline authors use appropriately inclusive language. In instances in which the guideline draws upon data based on research in a specified population (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

AFFILIATIONS

¹Emory University, Atlanta, GA

²American Society of Clinical Oncology (ASCO), Alexandria, VA

³Washington University School of Medicine, St Louis, MO

⁴University of Chicago Medical Center, Chicago, IL

⁵The University of Texas MD Anderson Cancer Center, Houston, TX

⁶Thomas Jefferson, Philadelphia, PA

⁷City of Hope Cancer Center, Atlanta, GA

⁸Fox Chase Cancer Center, Philadelphia, PA

⁹Hospital Sírio-Libanês, São Paulo, Brazil

¹⁰Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

¹¹George Washington University, Washington, DC

¹²Cleveland Clinic, Cleveland, OH

¹³Penn Medicine, Philadelphia, PA

¹⁴GBMC Health Care, Towson, MD

¹⁵Massachusetts General Hospital, Boston, MA

¹⁶University of Michigan Rogel Cancer Center, Ann Arbor, MI

¹⁷UPMC Hillman Cancer Center, Pittsburgh, PA

¹⁸Stanford University, Stanford, CA

CORRESPONDING AUTHOR

American Society of Clinical Oncology; e-mail: guidelines@asco.org.

EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each

recommendation. Additional information, including a supplement with additional evidence tables, clinical tools and resources, and links to patient information at www.cancer.org, is available at <https://ascopubs.org/topics/asco-guidelines/head-neck-cancer>.

EQUAL CONTRIBUTION

N.F.S. and B.M.B. were Expert Panel co-chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO-26-00235>.

AUTHOR CONTRIBUTIONS

Conception and design: All authors

Collection and assembly of data: All authors

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The Expert Panel wishes to thank Dr Helena Musau, Dr Susan Chang, and the Evidence Based Medicine Committee for their thoughtful reviews and insightful comments on this guideline.

REFERENCES

- Chen DW, Lang BHH, McLeod DSA, et al: Thyroid cancer. *Lancet* 401:1531-1544, 2023
- Song P, Pan G, Zhang Y, et al: Prospects and challenges of immunotherapy for thyroid cancer. *Endocr Pract* 31:373-379, 2025
- Higgins JPT, Thomas J, Chandler J et al (eds): *Cochrane Handbook for Systematic Reviews of Interventions* (ed 2). Chichester, United Kingdom, Wiley, 2019
- Balshem H, Helfand M, Schünemann HJ, et al: GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 64:401-406, 2011
- Sehgal K, Pappa T, Shin KY, et al: Dual immune checkpoint inhibition in patients with aggressive thyroid carcinoma: A phase 2 nonrandomized clinical trial. *JAMA Oncol* 10:1663-1671, 2024
- Mehnert JM, Varga A, Brose MS, et al: Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced, PD-L1-positive papillary or follicular thyroid cancer. *BMC cancer* 19:196, 2019
- Zhang Y, Zhang X, Lin L, et al: Efficacy and safety of targeted therapy for radioiodine-refractory differentiated thyroid cancer. *J Clin Endocrinol Metab* 110:873-886, 2025
- Busaidy NL, Konda B, Wei L, et al: Dabrafenib versus dabrafenib + trametinib in *BRAF*-mutated radioactive iodine refractory differentiated thyroid cancer: Results of a randomized, phase 2, open-label multicenter trial. *Thyroid* 32:1184-1192, 2022
- Leboulleux S, Cao CD, Zerdoud S, et al: A phase II redifferentiation trial with dabrafenib-trametinib and 131I in metastatic radioactive iodine refractory *BRAF* p.V600E-mutated differentiated thyroid cancer. *Clin Cancer Res* 29:2401-2409, 2023
- Brose MS, Cabanillas ME, Cohen EE, et al: Vemurafenib in patients with *BRAF*(V600E)-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: A non-randomised, multicentre, open-label, phase 2 trial. *Lancet Oncol* 17:1272-1282, 2016
- Tahara M, Kiyota N, Imai H, et al: A phase 2 study of encorafenib in combination with binimetinib in patients with metastatic *BRAF*-mutated thyroid cancer in Japan. *Thyroid* 34:467-476, 2024
- Jing R, Wu N, Wu Y, et al: Efficacy and safety of multikinase inhibitors for patients with refractory thyroid cancer: Systematic review and network meta-analysis. *J Clin Endocrinol Metab* 109:2658-2672, 2024
- Zhao M, Li R, Song Z, et al: Efficacy and safety of tyrosine kinase inhibitors for advanced metastatic thyroid cancer: A systematic review and network meta-analysis of randomized controlled trials. *Medicine* 103:e37655, 2024
- Yu J, Liu Z, Su Y, et al: Tyrosine kinase inhibitors for radioiodine refractory differentiated thyroid cancer: A systematic review and meta-analysis. *Clin Endocrinol* 100:379-388, 2024
- Su J, Wang M, Fu Y, et al: Efficacy and safety of multi-kinase inhibitors in patients with radioiodine-refractory differentiated thyroid cancer: A systematic review and meta-analysis of clinical trials. *Expert Rev Anticancer Ther* 22:999-1008, 2022
- Yan Z, Yang M, Lai CL: Clinical efficacy of lenvatinib for the treatment of radioiodine-refractory thyroid carcinoma: A systematic review and meta-analysis of clinical trials. *Clin Endocrinol* 95:478-488, 2021
- Oba T, Chino T, Soma A, et al: Comparative efficacy and safety of tyrosine kinase inhibitors for thyroid cancer: A systematic review and meta-analysis. *Endocr J* 67:1215-1226, 2020
- Feng G, Luo Y, Zhang Q, et al: Sorafenib and radioiodine-refractory differentiated thyroid cancer (RR-DTC): A systematic review and meta-analysis. *Endocrine* 68:56-63, 2020
- Tsoli M, Alexandraki KI, Spei ME, et al: Anti-tumor activity and safety of multikinase inhibitors in advanced and/or metastatic thyroid cancer: A systematic review and network meta-analysis of randomized controlled trials. *Horm Metab Res* 52:25-31, 2020
- Liu JW, Chen C, Loh EW, et al: Tyrosine kinase inhibitors for advanced or metastatic thyroid cancer: A meta-analysis of randomized controlled trials. *Curr Med Res Opin* 34:795-803, 2018
- Hadoux J, Elisei R, Brose MS, et al: Phase 3 trial of selipercatinib in advanced *RET*-mutant medullary thyroid cancer. *N Engl J Med* 389:1851-1861, 2023

22. Sherman SI, Clary DO, Elisei R, et al: Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. *Cancer* 122:3856-3864, 2016
23. Zheng X, Fang M, Fan Y, et al: Efficacy and safety of pralsetinib in Chinese advanced RET-mutant medullary thyroid cancer patients. *Endocr Relat Cancer* 31:e230134, 2024
24. Subbiah V, Hu MI, Mansfield AS, et al: Pralsetinib in patients with advanced/metastatic rearranged during transfection (RET)-altered thyroid cancer: Updated efficacy and safety data from the ARROW study. *Thyroid* 34:26-40, 2024
25. 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* 9:491-501, 2021
26. Wirth LJ, Sherman E, Robinson B, et al: Efficacy of selpercatinib in RET-altered thyroid cancers. *N Engl J Med* 383:825-835, 2020
27. Wirth LJ, Brose MS, Subbiah V, et al: Durability of response with selpercatinib in patients with RET-activated thyroid cancer: Long-term safety and efficacy from LIBRETTO-001. *J Clin Oncol* 42:3187-3195, 2024
28. Hamidi S, Yedururi S, Hu MI, et al: Efficacy and safety of selective RET inhibitors in patients with advanced hereditary medullary thyroid carcinoma. *Thyroid* 35:6-17, 2025
29. Hadoux J, Al Ghuzlan A, Lamartina L, et al: Patterns of treatment failure after selective rearranged during transfection (RET) inhibitors in patients with metastatic medullary thyroid carcinoma. *JCO Precis Oncol* 10.1200/PO.23.00053
30. Vuong HG, Ho ATN, Tran TTK, et al: Efficacy and toxicity of sorafenib in the treatment of advanced medullary thyroid carcinoma: A systematic review and meta-analysis. *Head Neck* 41:2823-2829, 2019
31. Schlumberger M, Elisei R, Müller S, et al: Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. *Ann Oncol* 28:2813-2819, 2017
32. Elisei R, Schlumberger MJ, Müller SP, et al: Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol* 31:3639-3646, 2013
33. Li D, Chi Y, Chen X, et al: Anlotinib in locally advanced or metastatic medullary thyroid carcinoma: A randomized, double-blind phase IIB trial. *Clin Cancer Res* 27:3567-3575, 2021
34. Wells SA Jr, Robinson BG, Gagel RF, et al: Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: A randomized, double-blind phase III trial. *J Clin Oncol* 30:134-141, 2012
35. 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* 15:717-726, 2019
36. Schlumberger M, Jarzab B, Cabanillas ME, et al: A phase II trial of the multitargeted tyrosine kinase inhibitor lenvatinib (E7080) in advanced medullary thyroid cancer. *Clin Cancer Res* 22:44-53, 2016
37. Ahmed M, Barbachano Y, Riddell A, et al: Analysis of the efficacy and toxicity of sorafenib in thyroid cancer: A phase II study in a UK based population. *Eur J Endocrinol* 165:315-322, 2011
38. Ravaud A, de la Fouchardière C, Caron P, et al: A multicenter phase II study of sunitinib in patients with locally advanced or metastatic differentiated, anaplastic or medullary thyroid carcinomas: Mature data from the THYSU study. *Eur J Cancer* 76:110-117, 2017
39. Uchino K, Komoda M, Tomomatsu J, et al: Safety and tolerability of vandetanib in Japanese patients with medullary thyroid cancer: A phase I/II open-label study. *Endocr Pract* 23:149-156, 2017
40. Bible KC, Suman VJ, Molina JR, et al: A multicenter phase 2 trial of pazopanib in metastatic and progressive medullary thyroid carcinoma: MC057H. *J Clin Endocrinol Metab* 99:1687-1693, 2014
41. Wells SA Jr, Gosnell JE, Gagel RF, et al: Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. *J Clin Oncol* 28:767-772, 2010
42. Koehler VF, Adam P, Frank-Raue K, et al: Real-world efficacy and safety of cabozantinib and vandetanib in advanced medullary thyroid cancer. *Thyroid* 31:459-469, 2021
43. Matrone A, Prete A, Nervo A, et al: Lenvatinib as a salvage therapy for advanced metastatic medullary thyroid cancer. *J Endocrinol Invest* 44:2139-2151, 2021
44. Brose MS, Nutting CM, Jarzab B, et al: Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: A randomised, double-blind, phase 3 trial. *Lancet* 384:319-328, 2014
45. Schlumberger M, Tahara M, Wirth LJ, et al: Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 372:621-630, 2015
46. Leboulleux S, Bastholt L, Krause T, et al: Vandetanib in locally advanced or metastatic differentiated thyroid cancer: A randomised, double-blind, phase 2 trial. *Lancet Oncol* 13:897-905, 2012
47. Sosa JA, Elisei R, Jarzab B, et al: Randomized safety and efficacy study of fosbretabulin with paclitaxel/carboplatin against anaplastic thyroid carcinoma. *Thyroid* 24:232-240, 2014
48. Iyer PC, Dadu R, Ferrarotto R, et al: Real-world experience with targeted therapy for the treatment of anaplastic thyroid carcinoma. *Thyroid* 28:79-87, 2018
49. Lee KK, Morris JC III, Kumar A, et al: Pemetrexed-carboplatin salvage therapy in advanced thyroid cancers. *Head Neck* 47:813-821, 2025
50. Hatashima A, Archambeau B, Armbruster H, et al: An evaluation of clinical efficacy of immune checkpoint inhibitors for patients with anaplastic thyroid carcinoma. *Thyroid* 32:926-936, 2022
51. Cabanillas ME, Dadu R, Ferrarotto R, et al: Anti-programmed death ligand 1 plus targeted therapy in anaplastic thyroid carcinoma: A nonrandomized clinical trial. *JAMA Oncol* 10:1672-1680, 2024
52. 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* 36:7-13, 2018
53. Subbiah V, Kreitman RJ, Wainberg ZA, et al: Dabrafenib plus trametinib in patients with BRAF V600E-mutant anaplastic thyroid cancer: Updated analysis from the phase II ROAR basket study. *Ann Oncol* 33:406-415, 2022
54. Subbiah V, Kreitman RJ, Wainberg ZA, et al: Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: The phase 2 ROAR trial. *Nat Med* 29:1103-1112, 2023
55. Capdevila J, Wirth LJ, Ernst T, et al: PD-1 blockade in Anaplastic thyroid carcinoma. *J Clin Oncol* 38:2620-2627, 2020
56. Chang CF, Yang MH, Lee JH, et al: The impact of BRAF targeting agents in advanced anaplastic thyroid cancer: A multi-institutional retrospective study in Taiwan. *Am J Cancer Res* 12:5342-5350, 2022
57. Lorimer C, Cheng L, Chandler R, et al: Dabrafenib and trametinib therapy for advanced anaplastic thyroid cancer—Real-world outcomes from UK centres. *Clin Oncol (R Coll Radiol)* 35:e60-e66, 2023
58. Zhao X, Wang JR, Dadu R, et al: Surgery after BRAF-directed therapy is associated with improved survival in BRAF(V600E) mutant anaplastic thyroid cancer: A single-center retrospective cohort study. *Thyroid* 33:484-491, 2023
59. Hamidi S, Iyer PC, Dadu R, et al: Checkpoint inhibition in addition to dabrafenib/trametinib for BRAF-mutated anaplastic thyroid carcinoma. *Thyroid* 34:336-346, 2024
60. Huang D, Zhang J, Zheng X, et al: Efficacy and safety of lenvatinib in anaplastic thyroid carcinoma: A meta-analysis. *Front Endocrinol* 13:920857, 2022
61. Cabanillas ME, Busaidy NL, Zafereo M, et al: Lenvatinib plus pembrolizumab for the treatment of patients with non-BRAF mutated anaplastic thyroid cancer: A single center, phase 2 clinical trial. *medRxiv*. 10.1101/2025.11.09.25339786
62. 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* 39:2359-2366, 2021
63. Higashiyama T, Sugino K, Hara H, et al: Phase II study of the efficacy and safety of lenvatinib for anaplastic thyroid cancer (HOPE). *Eur J Cancer* 173:210-218, 2022
64. Savvides P, Nagaiah G, Lavertu P, et al: Phase II trial of sorafenib in patients with advanced anaplastic carcinoma of the thyroid. *Thyroid* 23:600-604, 2013
65. 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* 97:3179-3184, 2012
66. Tahara M, Kiyota N, Yamazaki T, et al: Lenvatinib for anaplastic thyroid cancer. *Front Oncol* 7:25, 2017
67. Kim M, Ahn J, Song DE, et al: Real-world experience of lenvatinib in patients with advanced anaplastic thyroid cancer. *Endocrine* 71:427-433, 2021
68. Kim SY, Kim SM, Kim JW, et al: Survival with lenvatinib for the treatment of progressive anaplastic thyroid cancer: A single-center, retrospective analysis. *Front Endocrinol* 11:599, 2020
69. Capdevila J, Iglesias L, Halperin I, et al: Sorafenib in metastatic thyroid cancer. *Endocr Relat Cancer* 19:209-216, 2012
70. Iwasaki H, Toda S, Takahashi A, et al: Outcome of initial lenvatinib treatment in patients with unresectable anaplastic thyroid cancer. *Oncol Lett* 26:416, 2023
71. Iwasaki H, Toda S, Suganuma N, et al: Lenvatinib vs. palliative therapy for stage IVC anaplastic thyroid cancer. *Mol Clin Oncol* 12:138-143, 2020
72. Zheng X, Wang J, Ye T, et al: Efficacy and safety of anlotinib-based chemotherapy for locally advanced or metastatic anaplastic thyroid carcinoma. *Endocrine* 81:540-546, 2023
73. Brose MS, Robinson B, Sherman SI, et al: Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 22:1126-1138, 2021
74. Waguespack SG, Drilon A, Lin JJ, et al: Efficacy and safety of larotrectinib in patients with TRK fusion-positive thyroid carcinoma. *Eur J Endocrinol* 186:631-643, 2022
75. Doebele RC, Drilon A, Paz-Ares L, et al: Entrectinib in patients with advanced or metastatic *NTRK* fusion-positive solid tumours: Integrated analysis of three phase 1-2 trials. *Lancet Oncol* 21:271-282, 2020
76. Drilon A, Camidge DR, Lin JJ, et al: Repotrectinib in *ROS1* fusion positive non small-cell lung cancer. *N Engl J Med* 390:118-131, 2024
77. Wirth L, Gao M, Park YJ, et al: Efficacy and safety of dabrafenib plus trametinib (D+T) in patients with radioactive iodine (RAI)-refractory BRAF V600-mutant differentiated thyroid cancer (DTC). Presented at the 2025 European Society for Medical Oncology (ESMO) Congress; October 17-21, 2025; Berlin, Germany. Abstract 29870
78. Oh DY, Algazi A, Capdevila J, et al: Efficacy and safety of pembrolizumab monotherapy in patients with advanced thyroid cancer in the phase 2 KEYNOTE-158 study. *Cancer* 129:1195-1204, 2023
79. French JD, Haugen BR, Worden FP, et al: Combination targeted therapy with pembrolizumab and lenvatinib in progressive, radioiodine-refractory differentiated thyroid cancers. *Clin Cancer Res* 30:3757-3767, 2024
80. Shimaoka K, Schoenfeld DA, DeWys WD, et al: A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. *Cancer* 56:2155-2160, 1985
81. Baloch ZW, Asa SL, Barletta JA, et al: Overview of the 2022 WHO Classification of Thyroid Neoplasms. *Endocr Pathol* 33:27-63, 2022

82. Brose MS, Capdevila J, Elisei R, et al: Vandetanib in locally advanced or metastatic differentiated thyroid cancer refractory to radioiodine therapy. *Endocr Relat Cancer* 31:e230354, 2024
83. Sherman EJ, Dunn LA, Ho AL, et al: Phase 2 study evaluating the combination of sorafenib and temsirolimus in the treatment of radioactive iodine-refractory thyroid cancer. *Cancer* 123: 4114-4121, 2017
84. Kiyota N, Robinson B, Shah M, et al: Defining radioiodine-refractory differentiated thyroid cancer: Efficacy and safety of lenvatinib by radioiodine-refractory criteria in the SELECT trial. *Thyroid* 27: 1135-1141, 2017
85. Dierks C, Ruf J, Seufert J, et al: 1646MO Phase II ATLEP trial: Final results for lenvatinib/pembrolizumab in metastasized anaplastic and poorly differentiated thyroid carcinoma. *Ann Oncol* 33: S1295, 2022
86. Marczyk VR, Fazeli S, Dadu R, et al: NTRK fusion-positive thyroid carcinoma: From diagnosis to targeted therapy. *JCO Precis Oncol* 10.1200/PQ.24.00321
87. Cabanillas ME, Busaidy NL, Gunn GB, et al: Adjuvant pembrolizumab after upfront multimodal therapy for stage IVB anaplastic thyroid cancer. *Thyroid* 35:763-770, 2025
88. Madan RA: Phase II trial of pembrolizumab in recurrent or metastatic medullary thyroid cancer. 2017. <https://clinicaltrials.gov/study/NCT03072160>
89. Schlumberger M, Abdelmoumene N, Delisle MJ, et al: Treatment of advanced medullary thyroid cancer with an alternating combination of 5 FU-streptozocin and 5 FU-dacarbazine. The Groupe d'Etude des Tumeurs a Calcitonine (GETC). *Br J Cancer* 71:363-365, 1995
90. Nocera M, Baudin E, Pellegriti G, et al: Treatment of advanced medullary thyroid cancer with an alternating combination of doxorubicin-streptozocin and 5 FU-dacarbazine. Groupe d'Etude des Tumeurs a Calcitonine (GETC). *Br J Cancer* 83:715-718, 2000
91. Wu LT, Averbuch SD, Ball DW, et al: Treatment of advanced medullary thyroid carcinoma with a combination of cyclophosphamide, vincristine, and dacarbazine. *Cancer* 73:432-436, 1994
92. Filetti S, Durante C, Hartl DM, et al: ESMO clinical practice guideline update on the use of systemic therapy in advanced thyroid cancer. *Ann Oncol* 33:674-684, 2022
93. Gilligan T, Bohlke K, Alpert AB, et al: Patient-clinician communication: ASCO guideline update. *J Clin Oncol* 10.1200/JCO-26-00118 [epub ahead of print on March 10, 2026]
94. Hendren S, Chin N, Fisher S, et al: Patients' barriers to receipt of cancer care, and factors associated with needing more assistance from a patient navigator. *J Natl Med Assoc* 103:701-710, 2011
95. Alpert AB, Scout NFN, Schabath MB, et al: Gender- and sexual Orientation- based inequities: Promoting inclusion, visibility, and data accuracy in oncology. *Am Soc Clin Oncol Educ Book* 42:1-17, 2022
96. Levit LA, Byatt L, Lyss AP, et al: Closing the rural cancer care gap: Three institutional approaches. *JCO Oncol Pract* 16:422-430, 2020
97. Schnipper LE, Davidson NE, Wollins DS, et al: American Society of clinical oncology statement: A conceptual framework to assess the value of cancer treatment options. *J Clin Oncol* 33: 2563-2577, 2015
98. Schnipper LE, Davidson NE, Wollins DS, et al: Updating the American Society of Clinical Oncology value framework: Revisions and reflections in response to comments received. *J Clin Oncol* 34: 2925-2934, 2016
99. Streeter SB, Schwartzberg L, Husain N, et al: Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. *J Oncol Pract* 7:46s-51s, 2011
100. Dusetzina SB, Winn AN, Abel GA, et al: Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. *J Clin Oncol* 32:306-311, 2014
101. Meropol NJ, Schrag D, Smith TJ, et al: American Society of Clinical Oncology guidance statement: The cost of cancer care. *J Clin Oncol* 27:3868-3874, 2009
102. Anderson RT, Linnehan JE, Tongbram V, et al: Clinical, safety, and economic evidence in radioactive iodine-refractory differentiated thyroid cancer: A systematic literature review. *Thyroid* 23: 392-407, 2013
103. Wilson L, Huang W, Chen L, et al: Cost effectiveness of lenvatinib, sorafenib and placebo in treatment of radioiodine-refractory differentiated thyroid cancer. *Thyroid* 27:1043-1052, 2017
104. Fleeman N, Houten R, Bagust A, et al: Lenvatinib and sorafenib for differentiated thyroid cancer after radioactive iodine: A systematic review and economic evaluation. *Health Technol Assess* 24: 1-180, 2020
105. Tappenden P, Carroll C, Hamilton J, et al: Cabozantinib and vandetanib for unresectable locally advanced or metastatic medullary thyroid cancer: A systematic review and economic model. *Health Technol Assess* 23:1-144, 2019
106. Sanders JJ, Temin S, Ghoshal A, et al: Palliative care for patients with cancer: ASCO guideline update. *J Clin Oncol* 42:2336-2357, 2024
107. Koyfman SA, Ismaila N, Crook D, et al: Management of the neck in squamous cell carcinoma of the oral cavity and oropharynx: ASCO clinical practice guideline. *J Clin Oncol* 37:1753-1774, 2019
108. Maghami E, Ismaila N, Alvarez A, et al: Diagnosis and management of squamous cell carcinoma of unknown primary in the head and neck: ASCO guideline. *J Clin Oncol* 38:2570-2596, 2020
109. Chen YP, Ismaila N, Chua MLK, et al: Chemotherapy in combination with radiotherapy for definitive-intent treatment of stage II-IVA nasopharyngeal carcinoma: CSCO and ASCO guideline. *J Clin Oncol* 39:840-859, 2021
110. Geiger JL, Ismaila N, Beadle B, et al: Management of salivary gland malignancy: ASCO guideline. *J Clin Oncol* 39:1909-1941, 2021
111. Schünemann H, Brożek J, Guyatt G, et al (eds): GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group, 2013. guidelinedevelopment.org/handbook

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Systemic Treatment of Thyroid Cancer: ASCO Guideline

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](http://OpenPayments)).

Nabil F. Saba

Employment: Winship Cancer Institute

Honoraria: Exelixis, GlaxoSmithKline, Coherus Biosciences, Surface Oncology, Nanobiotix, BMS, Medscape, Merck, Summit Therapeutics, Johnson & Johnson/Janssen, Reddy Pharma Iberia

Consulting or Advisory Role: Akeso Biopharma

Research Funding: Bristol Myers Squibb, Exelixis

Patents, Royalties, Other Intellectual Property: UpToDate chapter writing and editing, Springer textbook royalty

Travel, Accommodations, Expenses: Merck

Nofisat Ismaila

Employment: GlaxoSmithKline (I)

Stock and Other Ownership Interests: GlaxoSmithKline (I)

Douglas Adkins

Consulting or Advisory Role: Merck, CUE Biopharma, Immunitas, Kura Oncology, Boehringer Ingelheim, Genmab/Seattle Genetics, Adlai Nortye, InhibRx, Merus, Purple Biotech, Regeneron, Adcendo, AstraZeneca, GlaxoSmithKline, Johnson & Johnson/Janssen, Pyxis, Tubulis GmbH

Research Funding: Pfizer (Inst), Lilly (Inst), Merck (Inst), Celgene (Inst), Novartis (Inst), AstraZeneca (Inst), Blueprint Medicines (Inst), Bristol Myers Squibb (Inst), Kura Oncology (Inst), CUE Biopharma (Inst), Cofactor Genomics (Inst), Debiopharm Group (Inst), ISA Pharmaceuticals (Inst), Gilead Sciences (Inst), BeiGene (Inst), Roche (Inst), Vaccinex (Inst), Immutep (Inst), Hookipa Biotech (Inst), Epizyme (Inst), Adlai Nortye (Inst), BioAtla (Inst), Boehringer Ingelheim (Inst), Calliditas Therapeutics (Inst), Genmab (Inst), NATCO Pharma (Inst), Tizona Therapeutics, Inc (Inst), Seagen (Inst), Merus (Inst), InhibRx (Inst), Erasca, Inc (Inst), Alentis Therapeutics (Inst), Coherus Biosciences (Inst), Takeda (Inst), Xilio Therapeutics (Inst), GlaxoSmithKline (Inst), Johnson & Johnson/Janssen (Inst), Rgenta (Inst), AVEO (Inst), Daiichi Sankyo Europe GmbH (Inst), Exelixis (Inst), Tempus (Inst)

Nishant Agrawal

Leadership: OrisDX

Stock and Other Ownership Interests: OrisDX, Privo Technologies

Speakers' Bureau: Merck

Patents, Royalties, Other Intellectual Property: Patent pending for salivary diagnostics to diagnose oral cancer

Open Payments Link: <https://openpaymentsdata.cms.gov/physician/656166>

Neil Akhave

Honoraria: American Society of Clinical Oncology, ASCO

Consulting or Advisory Role: Genmab/Seagen, Adcendo

Research Funding: Innocare (Inst), Bicara Therapeutics (Inst), Seagen (Inst), AVEO (Inst), Merus (Inst)

Travel, Accommodations, Expenses: American Society of Clinical Oncology, Genmab/Seagen, American Society of Clinical Oncology

Erik S. Blomain

Employment: Thomas Jefferson University

Research Funding: 10X genomics

Maria E. Cabanillas

Honoraria: Boston University, Yale University, Miami Cancer Research Center

Consulting or Advisory Role: Exelixis, Novartis, Thryv, Fore Biotherapeutics, Novartis

Research Funding: Eisai, Roche/Genentech, Exelixis, Merck

Thomas J. Galloway

Honoraria: UpToDate

Research Funding: Cardinal Health

Guilherme Harada

Honoraria: Lilly, Novartis, AstraZeneca, Merck Sharp Dohme, Bristol Myers Squibb, BeiGene, Daiichi Sankyo, Johnson & Johnson/Janssen, Takeda, Amgen

Salem I. Noureldine

Travel, Accommodations, Expenses: Taewoong

Joe Scharpf

Speakers' Bureau: Medtronic

Lova L. Sun

Consulting or Advisory Role: Genmab/Seagen, Bayer, Pfizer, AstraZeneca, GlaxoSmithKline, Merus, Guardant Health

Research Funding: Blueprint Medicines (Inst), Seagen (Inst), IO Biotech (Inst), Erasca, Inc (Inst), AbbVie (Inst), Immunocore (Inst), Frontier Medicines (Inst), Merus (Inst), ORIC Pharmaceuticals (Inst), Tempus (Inst)

Lori Wirth

Consulting or Advisory Role: Merck, Eisai, Lilly, Bayer, Coherus Biosciences, Bicara Therapeutics, Novartis, Coherus Biosciences, Fore Biotherapeutics, LEO Pharma, Pyxis, Tubulis GmbH, Summit Therapeutics

Research Funding: Checkmate Pharmaceuticals (Inst), Lilly (Inst), Eisai (Inst), Novartis (Inst), Ellipses Pharma (Inst), Ascendis Pharma (Inst)

Other Relationship: PDS Biotechnology

Francis Worden

Honoraria: Merck Sharp & Dohme, Eisai, Exelixis, Sun Pharma Advanced Research Company, PDS Biotechnology, Merus, Merus, Fore Biotherapeutics, Fore Biotherapeutics, Johnson & Johnson/Janssen, Johnson & Johnson/Janssen

Consulting or Advisory Role: Merck, Exelixis, Sun Pharma Advanced Research Company, Adlai Nortye, Coherus Biosciences, Coherus Biosciences, PDS Biotechnology, Fore Biotherapeutics, Johnson & Johnson/Janssen

Research Funding: Merck (Inst), CUE Biopharma (Inst), Loxo/Lilly (Inst), Adlai Nortye, PDS Biotechnology, Coherus Biosciences, EpicentRx

Travel, Accommodations, Expenses: Merck Sharp & Dohme, Sun Pharma Advanced Research Company

Dan P. Zandberg

Consulting or Advisory Role: Blueprint Medicines, MacroGenics, Prelude Therapeutics, Merck, InhibiRx, Seagen, Bicara Therapeutics, Coherus Biosciences, Coherus Biosciences

Research Funding: Merck (Inst), Bristol Myers Squibb (Inst), MacroGenics (Inst), Aduro Biotech (Inst), AstraZeneca (Inst), GlaxoSmithKline (Inst), Bicara Therapeutics (Inst), ISA Pharmaceuticals (Inst), Novasenta (Inst), AVEO (Inst)

Beth M. Beadle

Open Payments Link: <https://openpaymentsdata.cms.gov/search/physicians/by-name-and-location?firstname=Beth&lastname=beadle&city=&state=&zip=&country=&specialty=>

No other potential conflicts of interest were reported.

APPENDIX 1. GUIDELINE DISCLAIMER

The Clinical Practice Guidelines and other guidance published herein are provided by the ASCO, Inc to assist clinicians in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating clinician, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating clinician in the context of treating the individual patient. Use of the information is voluntary. ASCO does not endorse third party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a

brand or trade name is for identification purposes only. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at <http://www.asco.org/guideline-methodology>). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting, or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

TABLE A1. Thyroid Cancer Guideline Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Beth M. Beadle, MD (co-chair)	Stanford University, Stanford, CA	Radiation Oncology
Nabil Saba, MD (co-chair)	Emory University, Atlanta, GA	Medical Oncology
Douglas Adkins, MD	Washington University School of Medicine, St Louis, MO	Medical Oncology
Nishant Agrawal, MD	University of Chicago Medical Center, Chicago, IL	Surgical Oncology
Neil Akhave, MD	The University of Texas MD Anderson Cancer Center, Houston, TX	Medical Oncology
Anca M. Avram, MD	Case Western Reserve University School of Medicine, Cleveland, OH	Nuclear Medicine
Erik S. Blomain, MD, PhD	Thomas Jefferson, Philadelphia, PA	Radiation Oncology and Patient Representation
Maria E. Cabanillas, MD	The University of Texas MD Anderson Cancer Center, Houston, TX	Oncologic Endocrinologist
Amy Chen, MD	City of Hope Cancer Center, Atlanta, GA	Surgical Oncology
Thomas J. Galloway, MD	Fox Chase Cancer Center, Philadelphia, PA	Radiation Oncology
Guilherme Harada, MD	Hospital Sirio-Libanês, São Paulo, Brazil	Medical Oncology
Dapeng Li, MD	Tianjin Medical University Cancer Institute and Hospital, Tianjin, China	Surgical Oncology
Salem I. Noureldine, MD	George Washington University, Washington, DC	Surgical Endocrinology
Joe Scharpf, MD	Cleveland Clinic, Cleveland, OH	Medical Oncology
Lova L. Sun, MD	Penn Medicine, Philadelphia, PA	Medical Oncology
Mei Tang, MD	GBMC Health Care, Towson, MD	Community Oncologist
Lori Wirth, MD	Massachusetts General Hospital, Boston, MA	Medical Oncology
Francis Worden, MD	University of Michigan Rogel Cancer Center, Ann Arbor, MI	Medical Oncology
Dan P. Zandberg, MD	UPMC Hillman Cancer Center, Pittsburgh, PA	Medical Oncology
Nofisat Ismaila, MD	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

TABLE A2. Evidence Quality and Recommendation Rating Definitions

Term	Definitions
Evidence quality	
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention.
Conditional	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

NOTE. GRADE Handbook.¹¹¹