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ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer

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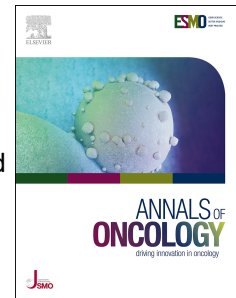
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ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer

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Highlights:

- This special article provides updated treatment recommendations on thyroid cancer.

- New targeted systemic therapies have now been approved for treating patients with advanced/metastatic thyroid cancers.
- This article summarises these new options and the order in which they should be used.
- Recommendations are based on available scientific data and the authors' collective expert opinion.
- Authorship includes a multidisciplinary group of thyroid cancer experts.

INTRODUCTION

Between 2013 and 2015, a number of multikinase inhibitors (MKIs) targeting the vascular endothelial growth factor receptor (VEGFR) were approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of advanced/metastatic differentiated thyroid cancers (DTCs) (i.e. lenvatinib and sorafenib) and medullary thyroid cancers (MTCs) (i.e. cabozantinib and vandetanib), thus becoming the standard first-line systemic therapy in this setting.¹ Head-to-head comparisons between the two pairs of drugs (i.e. lenvatinib versus sorafenib, and cabozantinib versus vandetanib) have never been undertaken, thus not allowing a hierarchy to be established between them. The use of these agents in a real-world setting is mainly influenced by the regulatory heterogeneity across countries. If all available, an individualised cost-effectiveness analysis that considers the differences in terms of effectiveness and safety profile helps to decide the order in which they should be used. After these MKIs entered the market, several studies emerged to verify and describe the drugs' benefit.²⁻⁴ Data on real-life experiences, taken all together, provide evidence of their clinical effectiveness, and produce data on safety profiles that mimic those reported by the randomised clinical trials (RCTs). Substantial differences, however, emerge among studies in the magnitude of MKI effects and the incidence of some adverse events. This can largely be explained by the heterogeneity across the studies in inclusion criteria, sample size (small series are more prone to be influenced by outliers), drug doses, lengths of follow-up, assessment of disease progression and analysis of the outcome measures. Given the toxicities associated with MKIs, clinicians sometimes prefer to start treatment at a lower than approved dose. A recent RCT compared the efficacy

and safety profile of lenvatinib at the approved starting dose (i.e. 24 mg per day) and at a lower starting dose (i.e. 18 mg per day) in a cohort of patients with metastatic/advanced DTC.⁵ Not surprisingly, the higher dose turned out to more effective, in that the objective response rate (ORR) was 57.3% [95% confidence interval (CI) 46.1%-68.5%] versus 40.3% (95% CI 29.3%-51.2%) in the lower dose group [odds ratio 0.50 (95% CI 0.26-0.96)]. The safety profile was comparable. Although these data cannot be generalised to the whole class of MKIs, it seems reasonable to state that the higher the dose, the greater the efficacy of these drugs. While this assumption supports using the MKIs' approved starting dose to maximise their efficacy, the choice should be individualised based on the patient's performance status and comorbidities.

The therapeutic scenario has now been enriched with new pharmacological strategies. This article focuses on the recent new systemic therapy updates for treating patients with advanced/metastatic DTCs, anaplastic thyroid cancers (ATCs) and MTCs as given in the ESMO Clinical Practice Guidelines on thyroid cancer.¹ The discussion is limited to those cases in whom the neoplasm has spread to the neck or to distant sites, and is not amenable to surgery or other locoregional therapy.

View the ESMO eUpdate here: <https://www.esmo.org/guidelines/endocrine-and-neuroendocrine-cancers/thyroid-cancer/eupdate-thyroid-cancer-treatment-recommendations>.

DIFFERENTIATED AND POORLY DIFFERENTIATED THYROID CANCER

Management of advanced/metastatic disease

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Cabozantinib. In September 2021, the FDA approved cabozantinib tablet for treating adults and adolescents aged ≥ 12 years with radioactive iodine (RAI)-refractory DTC who progressed during previous treatment with MKIs targeting the VEGFR (i.e. sorafenib or lenvatinib). The recommended dose is 60 mg orally once daily on an empty stomach (i.e. no food intake for at least 2 hours before and at least 1 hour after taking the drug). It is worth noting that cabozantinib capsule is also available on the market to treat advanced MTCs (140 mg once daily). The two formulations are not bioequivalent and should not be used interchangeably. The

approval decision was based on data from the phase III COSMIC-311 trial (NCT03690388), a global, randomised, double-blind, placebo-controlled, phase III trial conducted in patients aged ≥ 16 years with RAI-refractory DTC (papillary or follicular and their variants).⁶ Patients were randomised 2:1 to treatment with cabozantinib tablet (60 mg once daily) or placebo.

An objective response in the ORR intention-to-treat (ITT) population was achieved in ten (15%; 99% CI 5.8-29.3) of 67 patients in the cabozantinib group versus 0 (0%; 99% CI 0-14.8) of 33 in the placebo group ($P = 0.028$), but this did not meet the prespecified significance level ($\alpha=0.01$). Interim analysis of progression-free survival (PFS) in the ITT population revealed significant improvement in the cabozantinib arm versus placebo [median not reached (96% CI 5.7-not estimable) versus 1.9 months (96% CI 1.8-3.6); hazard ratio 0.22 (96% CI 0.13-0.36; $P < 0.0001$)]. The PFS benefit with cabozantinib was maintained across all pre-treated subgroup of patients (i.e. lenvatinib, sorafenib or two previous VEGFR MKIs).

Adverse effects were manageable and consistent with the known safety profile of cabozantinib. Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 71 (57%) of 125 patients receiving cabozantinib and 16 (26%) of the 62 receiving placebo: the most frequent were palmar-plantar erythrodysesthesia [13 (10%) versus 0]; hypertension [11 (9%) versus 2 (3%)] and fatigue [10 (8%) versus 0]. Serious TRAEs occurred in 20 (16%) of 125 patients in the cabozantinib arm and one (2%) of 62 patients in the placebo group. There were no treatment-related deaths.⁶ An initial dose reduction to manage adverse events was required by 56% of the patients in the experimental arm, while 22% required a secondary dose reduction. Five percent of patients experienced TRAEs leading to drug discontinuation.

Based on these findings, cabozantinib emerges as a new therapeutic option in patients that have progressed following treatment with MKIs. It is noteworthy that lenvatinib efficacy has been tested in naïve patients as well as in patients who had received one prior treatment regimen with a MKI (including sorafenib) with a 65% response rate, and a PFS benefit was observed in both subgroups.⁷ This makes cabozantinib and lenvatinib two potential choices for second-line treatment of patients who progress on sorafenib. The optimal sequence cannot be determined

based on currently available evidence. The decision should be individualised for each patient considering the likelihood of response and safety profile of the drug.

The selective RET inhibitors selpercatinib and pralsetinib. In 2020, two selective RET inhibitors were approved by the EMA and the FDA in different settings for the treatment of advanced/metastatic DTC harbouring a *RET* fusion gene.

Selpercatinib. Selpercatinib is a novel, small-molecule RET inhibitor. The recommended dose is 120 mg twice daily for patients weighing <50 kg or 160 mg twice daily for those weighing ≥50 kg.⁸

In May of 2020, the FDA granted accelerated approval to selpercatinib for treating patients aged ≥12 years who required systemic therapy for advanced/metastatic *RET* fusion-positive DTCs and were refractory to or ineligible for RAI therapy. Eight months later (December 2020), selpercatinib was also granted conditional marketing authorisation by the EMA for the treatment of advanced/metastatic *RET* fusion-positive DTCs. The drug was approved only for use in adults and only after previous treatment with an approved MKI (i.e. sorafenib, lenvatinib or both).

The EMA and FDA approvals were based on the results of a multicentre, open-label, multicohort clinical trial (LIBRETTO-001, NCT03157128) in patients with advanced *RET*-altered tumours of various types.⁸ Efficacy for the treatment of *RET* fusion-positive thyroid cancers (TCs) was evaluated in a small cohort of 27 individuals aged ≥12 years or older with follicular cell-derived carcinomas (papillary in 13 patients, poorly differentiated in three, anaplastic in two and Hürthle cell in one). *RET* fusion partners varied but CCDC6 was the most common. RAI therapy had been administered in all cases in which it was considered appropriate, but the disease had invariably proved to be RAI-refractory. Nineteen of the 27 patients had received one or more approved systemic drug therapies (i.e. lenvatinib, sorafenib and/or doxorubicin).

The main efficacy endpoints for this study were an objective response [complete or partial, as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) v.1.1] and the duration of the response.⁹ Both were assessed by a blinded independent review committee. The ORR for the 19 who had already received systemic drug therapy was 79% (95% CI 54%-94%), and 87% of the responding

patients had responses lasting ≥ 6 months. In the remaining eight patients, who had not received prior treatment (other than RAI, when appropriate), the ORR was 100% (95% CI 63%-100%), and six (75%) of the eight patients had responses lasting ≥ 6 months.^{8,9} Selpercatinib displayed activity across all histologic types of TC represented in the cohort (including one ATC) and regardless of the RET fusion partner (CCDC186, ERC1, KTN1 or RUFY3).⁹

Safety was assessed in the 702 patients who received selpercatinib for any type of RET-altered solid tumour in the LIBRETTO study. Ninety-five percent had received at least one dose of the drug at the recommended dosage of 160 mg twice a day. Sixty-five percent of the enrolled subjects were exposed to the drug for ≥ 6 months and 34% were exposed for >1 year.⁸

The most common grade ≥ 3 TRAEs were hypertension (18%), increased alanine aminotransferase (ALT) levels (9%) and increased aspartate aminotransferase (AST) levels (8%). Selpercatinib was permanently discontinued in 2% of patients owing to a TRAE (increased ALT in 0.4%, sepsis in 0.4%, increased AST in 0.3%, drug hypersensitivity in 0.3%, fatigue in 0.3% and thrombocytopaenia in 0.3%). In 42% of the patients, dosage interruptions were necessary due to a TRAE, the most common of which were increased ALT and/or AST levels. Overall, the most common TRAEs (those occurring in $\geq 25\%$ of the patients) were increases in AST or ALT, increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhoea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, oedema, decreased platelets, increased total cholesterol, rash, decreased sodium and constipation.⁹

Pralsetinib. Pralsetinib is the second selective RET kinase inhibitor that has been authorised for treating advanced or metastatic *RET* fusion-positive DTCs. The recommended dose in adults and paediatric patients 12 years and older is 400 mg orally once daily on an empty stomach (i.e. no food intake for at least 2 hours before and at least 1 hour after taking the drug).¹⁰

In December of 2020, the FDA granted pralsetinib accelerated approval for the treatment of *RET* fusion-positive DTCs with the same age and prior treatment status requirements specified for selpercatinib (see earlier Selpercatinib section). To date,

the EMA has not approved pralsetinib yet for this indication, although it has approved the drug for the treatment of *RET* fusion-positive non-small-cell lung cancers (NSCLCs).

The FDA approval was granted on the basis of the clinically important effects observed with pralsetinib in the ARROW study (NCT03037385), a multicentre, open-label, multicohort clinical trial in adults with *RET*-altered tumours of various types.¹¹ Efficacy for the treatment of *RET* fusion-positive DTC was evaluated in nine patients with papillary TCs that were RAI-refractory and already treated with systemic therapies.^{10,11} The main efficacy outcomes, ORR and duration of response, were assessed by a blinded independent review committee using RECIST v.1.1 criteria. The ORR was 89% (95% CI 52%-100%), and all of the responding patients had responses lasting ≥ 6 months.

The most common TRAEs to pralsetinib ($\geq 25\%$ of treated patients) were constipation, hypertension, fatigue, musculoskeletal pain and diarrhoea. The most common Grade 3-4 laboratory abnormalities ($\geq 2\%$) were decreased lymphocyte count, decreased neutrophil counts, decreased haemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased AST, increased ALT, decreased platelets and increased alkaline phosphatase.¹¹ TRAEs led to dose reduction in 46% of the patients (neutropaenia in 9%, lymphopaenia in 8%, anaemia in 6% and hypertension in 6%), dose interruptions in 54% (neutropaenia in 9%, asthaenia in 8%, hypertension in 8%, anaemia in 6%, diarrhoea in 6% and lymphopaenia in 6%) and treatment discontinuation in 4% (anaemia in 1%, pneumonia in 1%, acute respiratory distress syndrome and pneumonitis in 1% and blood creatinine phosphokinase increased in 1%).

The tropomyosin receptor kinase inhibitors larotrectinib and entrectinib.

Tropomyosin receptor kinase (TRK) inhibitors are considered potentially effective treatments for solid tumours harbouring functional neurotrophic tyrosine receptor kinase (*NTRK*) fusions (including TCs).

Larotrectinib. The TRK inhibitor larotrectinib received EMA and FDA approval in 2018-19 for the treatment of adult and paediatric patients with TRK fusion-positive solid tumours that are locally advanced or metastatic.¹ Approval was based on a

pooled analysis of three multicentre, open-label, single-arm clinical trials conducted on 55 patients with metastatic solid tumours harbouring an *NTRK* gene fusion. An update of efficacy and safety results, with a longer follow up and additional enrolment (159 patients, including the original cohort) has been reported.¹²

Larotrectinib was administered orally, at a dose of 100 mg twice daily for adults and 100 mg/m² twice daily (maximum of 100 mg per dose) for paediatric patients. The study cohort included 24 patients with a TC, whose ORR was 79% (95% CI 58%-93%). The most common grade 3 or 4 TRAEs were increased ALT (3%), anaemia (2%) and decreased neutrophil count (2%). Dose reduction and dose discontinuation because of TRAEs occurred in 13 (8%) and 2 (1%) of 159 patients, respectively.

Entrectinib. The TRK arsenal has been later expanded to include entrectinib, a potent inhibitor of TRKA, TRKB, TRKC, ROS1 and ALK that has been specially designed to cross the blood–brain barrier. Entrectinib was approved by the EMA (July 31, 2020) and the FDA (August 15, 2019) for treating adults and adolescents aged ≥12 years with (any type of) solid tumour harbouring a *NTRK* gene fusion, including TCs. The recommended dosage of the drug in adults is 600 mg orally once daily. For paediatric patients the recommended dosage is based on body surface area.

The decisions to authorise entrectinib for treatment of *NTRK* fusion-positive TCs were based on the assessment of an integrated efficacy-evaluable population consisting of 54 patients.¹³ Ten tumour types, with at least 19 distinct histologies, were treated. The most common were sarcoma (n=13, 24%), NSCLC (n=10, 19%) and mammary analogue secretory carcinoma of the salivary gland (n=7, 13%). Five (9%) of the tumours were TCs. Enrolment requirements included the absence of a known acquired resistance mutation, and the presence of disease that was metastatic (or such that surgical resection was likely to result in severe morbidity) and progressive (following treatment or in the absence of any satisfactory standard therapy). On the whole, 57% (95% CI 43.2%-70.8%) of the patients had an objective response. Response rates in the subset of patients with TC were 42.9%.¹⁴ The most common grade 3 or 4 TRAEs were increased weight (10%) and anaemia (12%). Doses were reduced or discontinued because TRAEs in 40% and 4% of the patients, respectively.

The optimal sequence of MKIs and selective kinase inhibitors in RAI-refractory, advanced/metastatic DTC cannot be determined based on currently available evidence. Currently, regulatory constraints represent the main decision-making factor in several countries. Where both therapeutic strategies are viable, several elements enter the decision-making algorithm: these include the expected treatment response, the drug safety profile, and patients' preference.

Recommendations

- In the United States, cabozantinib is an option to treat adults and adolescents aged ≥ 12 years with RAI-refractory advanced/metastatic DTCs that have progressed following treatment with MKIs [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 2; FDA approved, not EMA approved].
- In Europe, selpercatinib is an option to treat adults with advanced/metastatic *RET* fusion-positive DTCs who have already received MKI therapy with sorafenib, lenvatinib or both [V, B; ESMO-MCBS v1.1 score: 3; ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) score: I-B; EMA approved, not FDA approved for this indication].
- In the United States, selpercatinib is an option to treat adults and adolescents aged ≥ 12 years with RAI-refractory advanced/metastatic *RET* fusion-positive DTCs, regardless of whether or not they have received MKI therapy with sorafenib, lenvatinib or both [V, B; ESCAT score: I-B; FDA approved, not EMA approved for this indication].
- In the United States, pralsetinib is an option to treat adults and adolescents ≥ 12 years of age with advanced or metastatic *RET* fusion-positive DTC who require systemic therapy and are RAI-refractory [V, B; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B; FDA approved, not EMA approved].
- Larotrectinib is an option for the treatment of adults and adolescents aged ≥ 12 years with metastatic *NTRK* fusion-positive solid tumours, not amenable to surgery, that have progressed following treatment [V, B; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C; FDA and EMA approved].
- Entrectinib is an option for treating adults and adolescents aged ≥ 12 years with metastatic or unresectable *NTRK* fusion-positive solid tumours that have

progressed in spite of standard-of-care treatment [V, B]; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C; FDA and EMA approved].

- If a systemic therapy of advanced/metastatic DTCs is planned, a genetic test targeting actionable cancer mutations should be considered to individualise therapy. Next-generation sequencing (NGS) analysis is the preferred approach, if available [III, C].

Figure 4 has been updated with the following footnotes: e, f, g and h.

ATCs

Management of advanced/metastatic disease

Systemic therapy and personalised medicine

Locally advanced or metastatic ATCs harbouring the *BRAF* V600E mutation should be treated with the BRAF inhibitor dabrafenib (150 mg twice daily) plus the MEK inhibitor trametinib (2 mg once daily).¹ In the presence of other druggable mutations (*RET* and *NTRK* rearrangements), targeted therapy may be proposed (see discussion of selective RET inhibitors and NTRK inhibitors in section on DTC and poorly differentiated TC). When non-druggable mutations come out following the genetic test, immunotherapy is an alternative.¹ Spatalizumab, a humanised monoclonal antibody against the programmed cell death protein 1 (PD-1) receptor was tested in a phase II study including 42 locally advanced and/or metastatic ATCs. Patients received spatalizumab intravenously, at the dose of 400 mg every 4 weeks. Responses were observed in 19% of the patients, with higher response rates seen in those cases who had tumour biopsies positive for programmed death-ligand 1 (PD-L1) expression (29%).¹⁵ Other approaches should be tested within the context of a clinical trial.

Figure 5 has been updated (footnote g) to reflect the impact of the recent developments on the management of ATC patients.

MTC

Management of advanced/metastatic disease

Systemic therapy and personalised medicine

The selective *RET* inhibitors selpercatinib and pralsetinib. In 2020, two selective *RET* inhibitors were approved by the EMA and the FDA in different settings for the treatment of advanced/metastatic MTC harbouring a *RET* mutation.

Selpercatinib. In May of 2020, the FDA granted accelerated approval to selpercatinib for the treatment of adult and paediatric patients ≥ 12 years of age with advanced or metastatic *RET*-mutant MTC who require systemic therapy. In December 2020, the EMA approved the drug for advanced MTC in patients aged ≥ 12 years but only after prior treatment with cabozantinib or vandetanib or both.

Approvals by both agencies were granted on the basis of the clinically important effects on the ORR in a multicentre, open-label, multicohort clinical trial (LIBRETTO-001, NCT03157128) conducted in patients with *RET*-altered solid tumours.⁹ Efficacy for advanced or metastatic *RET*-mutant MTC was investigated in adults and paediatric patients (≥ 12 years of age). In the 55 patients whose MTCs had already been treated with cabozantinib, vandetanib or both, the ORR was 69% (95% CI 55% to 81%), and 76% of the responding patients had responses lasting ≥ 6 months. In the 88 vandetanib and cabozantinib naïve-patients with *RET*-mutant MTCs, the ORR was 73% (95% CI 62% to 82%), and 61% of the responses lasted ≥ 6 months. Selpercatinib displayed activity across the study cohort regardless of the *RET* mutation genotype.

For details on the recommended doses of selpercatinib and its safety profile (as analysed in the LIBRETTO-001 trial), see earlier section on selected *RET* inhibitors selpercatinib and pralsetinib under DTC and poorly differentiated TC.

Pralsetinib. Pralsetinib is the second selective *RET* kinase inhibitor that has been authorised for treating advanced or metastatic *RET*-mutant MTCs. In December 2020, the FDA granted pralsetinib accelerated approval for the treatment of adult and paediatric patients ≥ 12 years of age with advanced or metastatic *RET*-mutant MTC who require systemic therapy. The approval was based on the clinically important effects observed with pralsetinib in the ARROW study (NCT03037385), a

multicentre, open-label, multicohort clinical trial in adults with RET-altered tumours of various types.¹¹

Efficacy for the treatment of *RET*-mutant MTC was analysed in two subgroups defined on the basis of their prior treatment status. In the subgroup previously treated with cabozantinib or vandetanib (n=55, median number of prior therapies: 2), the ORR was 60% (95% CI 46-73), with 79% of patients having responses lasting ≥ 6 months. In the treatment-naïve subgroup, the ORR was 71% (95% CI 48-89], and 80% of the responses lasted ≥ 6 months.¹¹ Responses were observed regardless of *RET* mutation genotype.

For details on the recommended doses of pralsetinib and its safety profiles (as analysed in the ARROW trial), see earlier section on selected RET inhibitors selpercatinib and pralsetinib under DTC and poorly differentiated TC.

The best sequence of MKIs and selective kinase inhibitors to optimise the clinical benefit in advanced/metastatic MTC cannot be determined based on currently available evidence. Two multicentre, randomised, open-label, phase III clinical trials comparing selpercatinib (ClinicalTrials.gov Identifier: NCT04211337) and pralsetinib (ClinicalTrials.gov Identifier: NCT04760288) to cabozantinib or vandetanib are underway, and can hopefully answer this question.

Recommendations

- In Europe, selpercatinib is an option for the treatment of adults and adolescents ≥ 12 years with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib [V, B; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B; EMA approved, not FDA approved for this indication].
- In the United States, selpercatinib is an option to treat adult and paediatric patients ≥ 12 years of age with advanced or metastatic *RET*-mutant MTC who require systemic therapy [V, B; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B; FDA approved, not EMA approved for this indication].
- In the United States, pralsetinib is an option to treat adult and paediatric patients ≥ 12 years of age with advanced or metastatic *RET*-mutant MTC who

require systemic therapy [V, B; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B; FDA approved, not EMA approved].

- If a systemic therapy of advanced/metastatic MTCs is planned, a genetic test targeting *RET* mutations should be strongly considered to individualise therapy. Allelic specific real-time PCR or NGS analysis are the preferred methods to detect *RET* mutations [III, A].

Figure 7 has been updated with footnotes g and h to reflect the impact of these recent developments on the management of patients with MTC patients.

Table 8

The ESMO-MCBS table has been updated (Table 8). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. ESMO-MCBS v1.1¹⁶ was used to calculate scores for new therapies/indications approved by the EMA or the FDA (<https://www.esmo.org/guidelines/esmo-mcbs>).

Table 9

For personalised therapy approaches, ESCAT classifications¹⁷ need to be considered and have been included in the text and provided in a biomarkers and molecular targets for precision medicine table (new Table 9).

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CD has reported advisory boards for Eisai, Eli Lilly; DMH has received honoraria from Medtronic; SL has reported honoraria for advisory boards for Eisai, Lilly, Bayer and invited speaker for Eisai; LDL has reported advisory boards for MSD, Merck Serono and Eli Lilly and invited speaker for Eisai and consulting activity for Ipsen; KN has received honoraria as invited speaker from Eisai and nonremunerated advisory role for Ipsen; MGP has reported honoraria for advisory board for Eli Lilly and invited speaker for Roche; AB has received honoraria for advisory boards for Amgen, Astellas, Janssen, invited speaker for Amgen and institutional research funding from Astellas and Janssen; SF has declared no conflict of interest.

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Figure 4. Recommendations for management of RAI-refractory, advanced/metastatic DTC patients

Purple: general categories or stratification; white: other aspects of management; blue: systemic anticancer therapy.

DTC, differentiated thyroid cancer; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FDG-PET, [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography; FDA, Food and Drug Administration; FDG-PET-CT, [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography-computed tomography; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MKI, multikinase inhibitor; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; RAI, radioactive iodine; RECIST, Response Evaluation Criteria in Solid Tumours; TC, thyroid cancer; Tg, thyroglobulin; TgAb, serum thyroglobulin antibody.

^a A large tumour burden may warrant either a locoregional or systemic therapy.

^b As assessed by the RECIST v1.1 [reference 94 from the original guideline publication].

^c The trend overtime of serum Tg or TgAb levels and the uptake at FDG–PET may predict disease progression and outcome.

^d ESMO-MCBS v1.1 was used to calculate scores for new therapies/indications approved by the EMA or the FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. (<https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1>).

^e Pralsetinib is FDA approved for treating patients ≥12 years of age with advanced or metastatic *RET* fusion-positive TC. As for genetic testing, NGS analysis is the preferred approach if available.

^f ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.¹⁷

^g Selpercatinib is EMA approved for treating adults with advanced or metastatic *RET* fusion-positive TC who had already received lenvatinib or sorafenib. The FDA authorised selpercatinib for treatment of advanced *RET* fusion-positive thyroid TCs in patients ≥ 12 years of age and regardless of whether or not MKI therapy had already been tried. A NGS analysis is the preferred approach for *RET* fusion testing.

^h Entrectinib and larotrectinib have been approved by the EMA and the FDA for treating adults and adolescents aged ≥ 12 years with metastatic or unresectable *NTRK* fusion-positive thyroid carcinomas. Genetic testing should be done preferably by NGS analysis.

ⁱ Cabozantinib is FDA approved for treating adults and adolescents aged ≥ 12 years with RAI-refractory DTC that has progressed during previous treatment with MKIs.

Figure 5. Recommendations for management of ATC patients

Purple: general categories or stratification; red: surgery; turquoise: combination of treatments or other systemic treatments; green: radiotherapy; white: other aspects of management; blue: systemic anticancer therapy.

ATC, anaplastic thyroid cancer; ChT, chemotherapy; DTC, differentiated thyroid cancer; EBRT, external beam radiotherapy; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDG-PET-CT, [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography-computed tomography; IMRT, intensity-modulated radiotherapy; M0, no distant metastasis; M1, distant metastasis; MTC, medullary thyroid cancer; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; PS, performance status; R0, no residual tumour; R1, microscopic residual tumour; TC, thyroid cancer; TT, total thyroidectomy.

^a With at least a core biopsy. Cytology is not sufficient to exclude differential diagnoses such as lymphoma, medullary or poorly differentiated TC.

^b Staging must not delay definitive treatment.

^c Laryngectomy not appropriate. Elective tracheostomy should be avoided.

^d Concomitant ChT should be offered in patients who have good PS.

^e Preferably within 3 weeks of surgery. IMRT is the recommended approach.

^f A NGS analysis targeting cancer-associated genes is the preferred approach if available.

^g ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.¹⁷

^h In the presence of druggable mutations other than *BRAF V600E* (e.g. *RET* fusions, *NTRK* fusions), targeted therapy may be proposed (see discussion of selective RET inhibitors and NTRK inhibitors in section on DTC and poorly differentiated TC and section on MTC). Genetic testing should be done preferably by NGS analysis. In the absence of druggable mutations, immunotherapy is an alternative. Other approaches

should be tested within the context of a clinical trial. Palliative ChT may be proposed in the absence of other therapeutic approaches.

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Figure 7. Recommendations for post-operative management of MTC patients

Purple: general categories or stratification; white: other aspects of management; blue: systemic anticancer therapy.

CEA, carcinoembryonic antigen; Ctn, calcitonin; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MTC, medullary thyroid cancer; NGS, next-generation sequencing; PCR, polymerase chain reaction; RECIST, Response Evaluation Criteria in Solid Tumours; US, ultrasound.

^a Multimodality imaging should be used to identify and to follow locoregional and/or distant metastases (see Follow-up, long-term implications and survivorship section).

^b Based on own institution cut-off.

^c Serum Ctn and CEA doubling times are efficient tools for predicting tumour progression. Doubling times shorter than 24 months are associated with progressive disease [reference 149 from the original guideline publication].

^d Clinically relevant disease sites are rarely detected in patients with Ctn levels <150 pg/ml.

^e Stable or progressive disease according to RECIST 1.1 [reference 94 from the original guideline publication]. In patients with stable disease, a large tumour burden may warrant either a locoregional or systemic therapy.

^f ESMO-MCBS v1.1 was used to calculate scores for new therapies/indications approved by the EMA or the FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (<https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1>).

^g Pralsetinib has been FDA-approved for treating patients ≥12 years of age with advanced or metastatic *RET*-mutant MTC. NGS analysis is the preferred method to detect *RET* mutations if available.

^h ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.¹⁷

ⁱ Selpercatinib has been approved for the treatment of advanced or metastatic *RET*-mutant MTC by the EMA (only in adults previously treated with cabozantinib or vandetanib) and by the FDA (in adults and adolescents aged ≥ 12 and regardless of whether or not the patients had previously been treated with multikinase inhibitors). DNA quantitative PCR or NGS analysis are the preferred approaches for testing *RET* mutations.

Table 9. Biomarkers and molecular targets for precision medicines and corresponding ESCAT scores

Biomarker or genomic alteration	Method of detection	Drug match	ESCAT score^{a,b}
<i>BRAF</i> mutations ^{23,24}	Sanger sequencing or NGS	<i>BRAF</i> inhibitors (e.g. dabrafenib)	I-B
<i>NTRK</i> fusions ^{12,13}	Sanger sequencing or NGS	<i>NTRK</i> inhibitors (e.g. entrectinib, larotrectinib)	I-C
<i>RET</i> mutations in Medullary thyroid cancer and <i>RET</i> fusions in thyroid cancers ^{9,11}	Sanger sequencing or NGS	<i>RET</i> inhibitors (e.g. pralsetinib, selpercatinib)	I-B

ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO-MCBS, ESMO Magnitude of Clinical Benefit Scale; NGS, next generation sequencing.

^a ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.

^b I-A, alteration–drug match is associated with improved outcome with evidence from randomised clinical trials showing the alteration–drug match in a specific tumour type results in a clinically meaningful improvement of a survival endpoint; I-B, alteration–drug match is associated with improved outcome with evidence from prospective, non-randomised clinical trials showing that the alteration–drug match in a specific tumour type results in clinically meaningful benefit as defined by ESMO-MCBS v1.1; I-C,

alteration–drug match is associated with improved outcome with evidence from clinical trials across tumour types or basket clinical trials showing clinical benefit associated with the alteration–drug match, with similar benefit observed across tumour types; III-A, alteration–drug match is suspected to improve outcome based on patients with the specific alteration but in a different tumour type, with limited/absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types.¹⁷

Table 8. ESMO-MCBS table for new therapies/indications in thyroid cancer

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/ toxicity	ESMO-MCBS score ^a
DTC							
Cabozantinib ^b	Adult and paediatric patients 12 years of age and older with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are RAI-refractory or ineligible	COSMIC-311 ⁶ Phase III NCT03690388	Placebo Median PFS: 1.9 months	PFS gain: 6.7 months ^c	PFS: 0.22 (0.13-0.36) ^d	Increased toxicity	2 (Form 2b)
Entrectinib	Adult and paediatric patients 12 years of age and older with solid tumours	STARTRK-1; STARTRK-2; ALKA-372-001 ¹³	Single arm	ORR: 57%			3 (Form 3)

	expressing an <i>NTRK</i> gene fusion, who have disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have not received a prior <i>NTRK</i> inhibitor, and who have no satisfactory treatment options	Phase I/II NCT02097810 NCT02568267 EudraCT 2012-000148-88		Median DoR: 10.4 months Median PFS: 11.2 months			
Larotrectinib	Adult and paediatric patients with solid tumours that display an <i>NTRK</i> gene fusion, who have disease that is locally advanced, metastatic or where	Studies of larotrectinib in patients with <i>NTRK</i> fusion-positive tumours (including	Single arm	ORR: 79% Median DoR: 35.2 months			3 (Form 3)

	surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options	SCOUT and NAVIGATE) ^{18,12} Phase I/II NCT02122913 NCT02637687 NCT02576431		Median PFS: 28.3 months			
Lenvatinib	Adult patients with progressive, locally advanced or metastatic DTC, refractory to RAI	SELECT ⁷ Phase III NCT01321554	Placebo Median PFS: 3.6 months	PFS gain: 14.7 months OS immature, not significant	PFS: 0.21 (0.14-0.31) ^e	>2% treatment-related deaths	2 (Form 2b)
Pralsetinib ^b	Adult and paediatric patients 12 years of age and older with advanced or	ARROW ¹¹ Phase I/II	Single arm	ORR: 89%			3 (Form 3)

	metastatic <i>RET</i> fusion-positive thyroid cancer who require systemic therapy and who are RAI-refractory	NCT03037385		Projected DoR: >9 months			
Selpercatinib ^f	Adults with advanced <i>RET</i> fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib	LIBRETTO-001 (Cohort 1) ⁹ Phase I/II NCT03157128	Single arm	ORR: 79% Median PFS: 20.1 months Median DoR: 18.4 months			3 (Form 3)
Sorafenib	Patients with progressive, locally advanced or metastatic DTC, refractory to RAI	DECISION ¹⁹ Phase III NCT00984282	Placebo	Median PFS: 5.8 months	PFS gain: 5.0 months PFS: 0.59 (0.45-0.76)	Increased toxicity	2 (Form 2b)

				OS immature, not significant			
MTC							
Cabozantinib	Adult patients with progressive, unresectable locally advanced or metastatic MTC	EXAM ^{20,21} Phase III NCT00704730	Placebo Median PFS: 4 months	PFS gain: 7.2 months	PFS: 0.28 (0.19-0.40)		3 (Form 2b)
Pralsetinib ^b	Adult and paediatric patients 12 years of age and older with advanced or metastatic <i>RET</i> -mutant MTC who require systemic therapy	ARROW ¹¹ Phase I/II NCT03037385	Single arm	ORR: 71% first line; 60% later line Projected DoR: >12 months			3 (Form 3)
Selpercatinib ⁹	Adults and adolescents 12 years and older with advanced <i>RET</i> -	LIBRETTO-001 (Cohort 3) ⁹	Single arm	ORR: 69%			3 (Form 3)

	mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib	Phase I/II NCT03157128		Median DoR: >12 months			
Selpercatinib ^h	Adult and paediatric patients 12 years of age and older with advanced or metastatic <i>RET</i> -mutant MTC who require systemic therapy	LIBRETTO-001(Cohort 4) ⁹ Phase I/II NCT03157128	Single arm	ORR: 73% Median DoR: 22.0 months			3 (Form 3)
Vandetanib	Aggressive and symptomatic MTC in adults, children and adolescents aged 5 years and over with unresectable locally	ZETA ²² Phase III NCT00410761	Placebo Median PFS: 19.3 months	PFS gain: 11.2 months (reported estimate)	PFS: 0.46 (0.31-0.69)	Increased toxicity	2 (Form 2b)

	advanced or metastatic disease			OS immature, not significant			
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CI, confidence interval; DoR, duration of response; DTC, differentiated thyroid cancer; EMA, European Medicines Agency; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; HR, hazard ratio; MTC, medullary thyroid cancer; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; OS, overall survival; PE, point estimate; PFS, progression-free survival; QoL, quality of life; RAI, radioactive iodine; VEGFR, vascular endothelial growth factor receptor.

^a The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. ESMO-MCBS v1.1¹⁶ was used to calculate scores (<https://www.esmo.org/guidelines/esmo-mcbs>).

^b FDA approved but not EMA approved.

^c Calculated estimate of gain based on PE HR 0.22.

^d 96% CI.

^e 99% CI.

^f The ESMO-MCBS score is based on data from previously treated patients with RET fusion-positive thyroid cancer included in the LIBRETTO-001 trial (n=19); these data formed the basis of the EMA approval in this setting. Data for previously untreated patients with RET fusion-positive thyroid cancer, which are included in the FDA licensed indication, are not currently published in a peer reviewed publication and are therefore not eligible for ESMO-MCBS scoring

^g EMA approved but not FDA approved in the second-line setting.

^h FDA approved but not EMA approved in the first-line setting.

