Clinical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Guidelines

Guidelines on the Use of Systemic Therapy in Patients with Advanced Thyroid Cancer

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Abstract

With increasing understanding of the molecular alterations leading to thyroid cancers in recent years we have seen a rapid increase in the number of effective targeted systemic therapies available for patients with advanced thyroid cancer; firstly with the advent of the multi-kinase inhibitors and more recently with more specific RET, BRAF, MEK, ALK and NTRK inhibitors. Although these developments are very welcome, they have resulted in a paradigm shift in the management of advanced thyroid cancer to which thyroid oncologists have had to rapidly adapt, learning how to supervise treatment safely with novel agents, the management of novel toxicities, when and how to arrange molecular genetic testing of cancers and, perhaps most importantly, determining when the optimum time is to start these treatments in what can often be a relatively indolent, if progressive, disease. We hope that these guidelines will support clinicians in making these decisions with their patients, as well as signposting and providing useful supporting information both for patients and clinicians.

Key words: Molecular genetics; multi-kinase inhibitors; patient information; thyroid cancer

Introduction

Iodine Refractory Differentiated Thyroid Cancer and Medullary Thyroid Cancer

Differentiated thyroid cancer (DTC) is the most common form of thyroid cancer, comprising papillary, follicular and Hürthle cell cancers. Most of these cancers are cured by a combination of surgery and radioiodine therapy. A proportion of patients with advanced disease will become refractory to radioiodine, a situation known as iodine-refractory DTC. These patients have a much worse prognosis.

Medullary thyroid cancer (MTC) is a rare subtype of thyroid cancer, accounting for around 5% of all thyroid cancers. It can arise as part of an inherited syndrome (multiple endocrine neoplasia type 2 or familial MTC) in around 25% of cases. These syndromes are a result of germline mutations in the RET gene. The remaining 75% of cases, which are sporadic, have a high incidence of somatic RET mutations. Although a proportion of patients are cured with surgery, recurrent and metastatic disease is relatively common.

Until recently, treatment options for these groups were very limited. Conventional cytotoxic chemotherapy has little activity. The advent of multi-kinase inhibitors (MKIs) and, more recently, more specifically targeted inhibitors has transformed the management of these patients.

General Principles

At what Stage Should Patients be Referred to an Oncologist for Discussion?

If not already under the care of an oncologist, patients with DTC should be referred at the point at which they are deemed to have developed radioiodine-refractory disease. Patients with MTC who have either measurable radiological disease or persistently detectable or rising calcitonin (even in

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https://doi.org/10.1016/j.clon.2022.10.009
0936-6555/

Please cite this article as: Wadsley J et al., Guidelines on the Use of Systemic Therapy in Patients with Advanced Thyroid Cancer, Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.009

the absence of radiological disease) should also be referred to meet an oncologist and discuss systemic therapy, although patients with asymptomatic stable or slowly progressing disease may then continue routine follow-up under other clinical teams, such as endocrinology.

The decision to commence systemic therapy and the timing of that treatment are individualised. It may be appropriate for patients to undergo a period of active surveillance before starting systemic therapy. During that time, it is important for a strong relationship to develop between the patient and the clinical team to allow both parties to be confident that monitoring is safe, to increase the likelihood that subtle changes in the patient's condition will be detected to allow timely initiation of treatment and to ensure that the patient's general condition is optimised prior to commencing therapy.

Options for systemic therapy include MKIs, RET inhibitors and NTRK inhibitors. At present, MKIs remain the first-line treatment, with RET inhibitors and NTRK inhibitors reserved for second-line use in selected patients who have proven gene alterations.

Testing for Genetic Alterations

With the advent of more specifically targeted treatments, dependent on the presence of particular genetic alterations, it is important that thyroid cancer multidisciplinary teams have access to the relevant molecular testing for patients with advanced disease, to determine the relevant treatment options.

A network of National Health Service (NHS) genomic laboratory hubs capable of molecular testing for RET mutations, BRAF mutations, RET and NTRK fusions has been set up in England. The hubs are strategically located in order to provide equitable access to molecular testing across the country. The National Genomic Test Directory [1] outlines which tests are available and funded by NHS England, and the list will be updated annually. The All Wales Medical Genomics Service offers an equivalent service in Wales. In Scotland, the Molecular Pathology Consortium provides molecular testing in four sites across Scotland. The range of tests offered is currently limited but under discussion with National Service Division (NSD) and will probably be updated following review of RET and NTRK inhibitors by the Scottish Medicines Consortium.

It is advised that molecular testing is undertaken at the point of diagnosis of advanced disease. Although the RET and NTRK inhibitors are currently used in the second-line setting, it is useful to know in advance if the patient has a gene alteration that may be a target for subsequent treatment.

Deciding when to Start Treatment

Patients with advanced radioactive iodine (RAI)-refractory DTC or metastatic/locally advanced MTC often have slowly progressive and asymptomatic disease, and many patients will continue to lead active lives. There is evidence that MKIs improve progression-free survival [2–5], but not overall survival. It should be noted that lack of overall survival benefit in these studies may be a result of crossover from placebo to the active drug and/or overall survival data being immature. A subsequent subgroup analysis of the SELECT data has shown an overall survival advantage for patients over the age of 65 years treated with lenvatinib [6].

Initiation of MKIs requires careful and regular monitoring, with the need for frequent clinic visits, blood tests and scans. Active surveillance may be appropriate for a proportion of patients. In addition, other targeted local treatments, such as external beam radiotherapy, stereotactic ablative body radiotherapy, embolisation and surgery, may control symptomatic and progressive lesions in the context of stable disease elsewhere, and delay the need for systemic therapy.

When deciding on a management strategy, both patient and disease factors should be considered. Some patients will have anxieties about surveillance strategies, whereas others do not wish to embark on treatment due to the need for frequent monitoring and risk of toxicity. The location and burden of disease should be taken into consideration, for example patients with disease near critical structures may benefit from earlier treatment, whereas those with small volume disease that is not likely to lead to imminent complications could be monitored [7]. The recommendation is that systemic therapy is introduced at the point at which the patient is deemed to be developing more rapidly progressive or symptomatic disease. The challenge is to identify this time point so as not to miss the window of opportunity to treat [8]. It is prudent to monitor patients carefully so that they do not develop impaired renal or liver function, or deteriorate in performance status, which may preclude optimal dose intensity. Patients should be reviewed every 3–4 months to assess symptoms and perform blood tests, including tumour marker (thyroglobulin for DTC and calcitonin and carcinoembryonic antigen for MTC). A radiological assessment should be carried out at the discretion of the clinical team. Initially this should be at least every 6 months, sooner if a change in symptom is noted or if there is an increase in the rate of rise of tumour markers. The frequency of imaging can be reduced if it becomes clear that the disease is stable.

Which Drug to Use?

Advanced Radioiodine-Refractory Differentiated Thyroid Cancer

In England and Wales, lenvatinib and sorafenib have both been approved by the National Institute for Health and Care Excellence (NICE) for use in this setting [9]. The guidance states that 'Lenvatinib and sorafenib are recommended as options for treating progressive, locally advanced or metastatic DTC (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine, only if:

- they have not had a tyrosine kinase inhibitor before or

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- they have had to stop taking a tyrosine kinase inhibitor within 3 months of starting it because of toxicity (specifically, toxicity that cannot be managed by dose delay or dose modification).'

The implication of this guidance is that clinicians will decide which MKI to use, and it is anticipated that the patient will not be treated with the other MKI unless they develop toxicity as described above.

Selpercatinib is currently available via the Cancer Drugs Fund for the treatment of advanced RET-altered DTC, in the second-line setting.

Larotrectinib and entrectinib are NTRK fusion inhibitors approved by NICE for the treatment of patients with solid tumours that display a NTRK gene fusion who have locally advanced or metastatic disease and who have no satisfactory alternative treatment options [10,11].

Although RET and NTRK inhibitors are currently only available in the second-line setting, it is recommended that molecular testing for RET and NTRK fusions is arranged at diagnosis of iodine-refractory disease, so that the full range of treatment options for an individual patient is understood from the outset.

Advanced Medullary Thyroid Cancer

A NICE review in 2018 concluded that cabozantinib would be approved for use in England and Wales [12], but not vandetanib [13]. In practice, cabozantinib and vandetanib have distinct toxicity profiles, and there may be some patients for whom one drug is more appropriate than the other. For example, cabozantinib is associated with an increased risk of fistulae and caution is recommended in patients with a history of inflammatory bowel disease, gastrointestinal bleeding or heavily pretreated areas of disease. Vandetanib should not be used in patients with congenital long QTc syndrome, a history of torsades de pointes, bradyarrhythmias or uncompensated heart failure.

Selpercatinib is currently available via the Cancer Drugs Fund for the second-line treatment of advanced RET-mutant MTC. A clinical trial of its use in the first-line setting, in comparison with current standard of care (cabozantinib or vandetinib) is ongoing.

Although a RET inhibitor is currently only available routinely in the second-line setting, it is recommended that molecular testing for somatic RET mutations is arranged at diagnosis of advanced disease, so that the full range of treatment options for an individual patient is understood from the outset.

See Supplementary Materials for more detailed information about individual drugs.

Biomarkers to Predict Benefit

Treatment emergent hypertension has been shown to be associated with superior progression-free and overall survival in patients with radioiodine-refractory DTC receiving lenvatinib [14]. There is no other evidence to date that any biomarkers are able to reliably predict benefit (or lack of benefit) from MKIs.

Data from the EXAM trial [5] suggest that patients with MTC with RET M918T mutations may derive more benefit than other patients from cabozantinib, but this information does not exclude patients without the mutation from receiving the treatment.

Patients with RET mutations (MTC), RET or NTRK fusions may benefit from treatment with specific RET or NTRK inhibitors.

Preparing Patients for Treatment

During the period of active surveillance, treatment with MKI can be discussed with the patient and specific patient information provided so that when the time comes to start treatment the patient and family are familiar with the options, including the relative benefits and possible toxicity.

Once the decision to commence treatment has been made, the patient should undergo, as a minimum, the following pretreatment tests/assessments:

- blood pressure
- ECG
- baseline N-terminal pro brain natriuretic peptide (BNP) and echocardiogram if concerns about cardiac status
- review of medications, e.g. concomitant drugs that may lead to QTc prolongation
- bloods – full blood count (FBC), renal, liver and bone profile, magnesium (Mg), thyroid function tests (TFTs), BNP, thyroglobulin (Tg) or calcitonin
- urinalysis for protein (all MKIs)
- computed tomography brain, neck, thorax, abdomen, pelvis

If the patient is found to be hypertensive or have electrolyte abnormalities, these should be controlled/corrected prior to commencing treatment.

Patient and General Practitioner Information Needs

Patients should have access to written information about the specific treatment, including practical aspects of how and when the drug should be taken, likely benefit, possible toxicity, concomitant drugs to avoid and simple measures they can take to minimise toxicity. They should have access to and contact details for a thyroid clinical nurse specialist (CNS) and should be informed how to seek help out of hours if they are concerned about toxicity.

See Supplementary Materials for details of helpful patient websites and patient information leaflet about thyroid genomics.

The general practitioner must be kept fully informed about the treatment plan. They should be provided with a clear and simple summary that should include:

- the indication for treatment
- brief description of the treatment
- the likely benefits

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- possible toxicity
- drugs to avoid
- follow-up arrangements
- clear instructions for any additional monitoring required, e.g. Blood pressure
- oncology team contact details for queries

Monitoring on Treatment

Treatment with MKIs is associated with frequent and sometimes severe toxicity. In some cases there will need to be a dose interruption until the toxicity improves/resolves. There is recent evidence that patients with shorter dose interruptions gained more benefit than those with longer interruptions [15]. It is therefore crucial to monitor patients carefully and proactively manage toxicity in order to reduce the need for long dose interruptions. Blood pressure can increase within the first week of treatment. If possible, patients should be encouraged to use a home blood pressure monitor and they should be provided with contact details for the clinical team to report the results.

Treatment with RET inhibitors or NTRK inhibitors appear to be better tolerated than with MKIs, but these drugs are also associated with toxicity and careful monitoring is still essential.

At each clinic visit the following should be performed as a minimum:

- review of symptoms and side-effects
- focused clinical examination
- bloods – FBC, renal, liver and bone profile, Mg, TFTs, Tg or calcitonin/carcinoembryonic antigen
- blood pressure
- ECG
- urinalysis
- prescription of any supportive treatments
- other required assessments for the specific therapy, e.g. monitoring of cardiac function and uric acid for patients taking entrectinib, monitoring of any visual changes for patients taking dabrafenib and trametinib.

The frequency of clinical review will vary according to the individual patient, but the initial schedule detailed in Table 1 is suggested. Follow-up beyond this can be 4 weekly, with scans every 12 weeks initially.

See Supplementary Material for drug assessment templates.

Management of Common Toxicities of Multi-Kinase Inhibitors

Diarrhoea

Prompt management of grade 1/2 diarrhoea can avoid more serious problems and avoid dose interruption. Implement dietary adjustments, for example reduce caffeine, dairy products, fatty or high fibre foods. This is unlikely to be sufficient, and early use of antidiarrhoeal agents is recommended. Loperamide should be prescribed alongside MKIs, and patients advised to take 4 mg after the initial loose stool, then 2 mg after each additional loose stool, or 4 hourly. Other measures include taking loperamide prophylactically 30 min before each dose of MKI, and the use of opioids or bile acid sequestrants such as cholestyramine. Renal function, electrolytes and ECG should be monitored more frequently whilst diarrhoea is ongoing.

In the case of grade 3 diarrhoea, treatment may need to be interrupted until symptoms have resolved and when restarting MKI a dose reduction should be considered.

Diarrhoea may also be a disease-related symptom in advanced MTC.

Table 1
Recommended schedule for clinical review of patients receiving targeted therapies for advanced thyroid cancer.

Week	Clinical assessment	Bloods, ECG, blood pressure, urinalysis	Imaging
1	✓	✓	-
2	✓	✓	-
4	✓	✓	-
6	If required	If required	-
8	✓	✓	-
12	✓	✓	✓

Fatigue

General supportive and lifestyle measures, including exercise, can improve fatigue. Enquire about coexistent psychological concerns. Increased thyroxine requirement is common on MKIs. Check thyroid function and increase levothyroxine dose if needed. Taking the MKI at night may help fatigue. A short treatment break or dose reduction may be necessary.

Hypertension

In patients with pre-existing hypertension (systolic blood pressure >150mHg), blood pressure should be controlled prior to starting treatment. Hypertension may develop within a week of commencing MKIs, so blood pressure should be monitored regularly, ideally daily.

Treatment-emergent hypertension should be managed aggressively and proactively. Examples of appropriate antihypertensives include ramipril or other ACE inhibitors, adding amlodipine or other calcium channel blocker and/or diuretics if required. If blood pressure is still not controlled

Table 2
Recommended sequence of management of hypertension in patients receiving targeted therapies for advanced thyroid cancers.

Step	Drug class	Dose
1	ACE inhibitor, e.g. Ramipril	2.5 mg, increasing to 5 mg
2	Amlodipine	5 mg, increasing to 10 mg
3	Refer for cardiology opinion	

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Table 3
Grading of proteinuria by 24 hour urinary protein and urine protein/creatinine ratio.

Grade	Proteinuria	Urine protein/creatinine ratio
1	1+ Urinary protein ≥ULN - < 1.0 g/24 h	<100 mg/mmol
2	2+ Urinary protein 1.0 - < 3.5 g/24 h	100–300 mg/mmol
3	3+ Urinary protein >3.5 g/24 h	>300mg/mmol
4	Nephrotic syndrome	

ULN, upper limit of normal.

on a combination of antihypertensives, cardiology advice should be sought (see Table 2).

Proteinuria

This is a particular problem with VEGR-targeted MKIs, for which regular monitoring of urine for protein is mandatory. It is frequently associated with hypertension, which should be managed aggressively. Dip stick testing is appropriate for initial monitoring, but if >2+ proteinuria is documented a more formal measurement by either 24 h urine collection or urine protein:creatinine ratio should be undertaken. In the case of grade 3 proteinuria, the MKI should be interrupted until resolved to grade 1 or less. In the case of chronic persistent proteinuria, the MKI should be stopped and referral to a nephrologist considered (see Table 3).

QTc Prolongation

This is a particular issue with vandetanib, although it can occasionally occur with other MKIs. Vandetanib should not be used in patients with congenital long QTc syndrome, a history of torsades de pointes, bradyarrhythmias or uncompensated heart failure. An ECG should be obtained prior to commencing treatment, and vandetanib should not be started in patients whose QTc interval is >480 ms. The ECG should be repeated at 2, 4, 8 and 12 weeks after commencing vandetanib, then 4 weekly as long as the patient remains on vandetanib. If the patient has persistent diarrhoea or known electrolyte abnormalities (potassium, calcium, magnesium), the ECG should be monitored more frequently. A single value of QTc interval ≥500 ms should lead to interruption of vandetanib, restarting at a reduced dose when the QTc interval has returned to baseline or <450 ms. Avoid concomitant use of other agents also known to prolong the QTc interval (see Table 4).

Table 4
Concomitant medications which may prolong QTc interval.

Antibiotics	Azithromycin, clarithromycin, erythromycin, roxithromycin, metronidazole (with alcohol), moxifloxan
Antifungals	Ketoconazole
Antihistamines	Terfenidine
Antivirals	Nelfinavir
Antimalarials	Chloroquine, mefloquine
Anaesthetics	Halothane
Anti-arrhythmics	Disopyramide, procainamide, quinidine, amiodarone, sotalol
Antidepressants	Amitriptyline, clomipramine, imipramine, dothiepin, doxepin
Antipsychotics	Risperidone, fluphenazine, haloperidol, clozapine, thioridiazine, ziprasidone, pimozide, droperidol
Other	Probucol, cisapride

Skin Toxicity

General skin care advice should be given to all patients commencing MKIs, and emollients should be routinely prescribed for the management of mild skin toxicity. A number of skin complaints can occur. Patients with unusually severe symptoms should be referred early for a dermatology opinion.

Palmar Plantar Syndrome

This can significantly impair quality of life and needs to be managed proactively. Emollients should be applied particularly to hands and feet from the start of treatment, and hands and feet should be inspected at clinic visits. Urea-based creams can be helpful for patients with evidence of hyperkeratosis. Patients should consider using cotton-lined or rubber gloves when washing dishes, and they should avoid wearing tight fitting shoes. In severe cases a treatment interruption and dose reduction should be considered.

Acneiform Rash

Mild cases can be managed with emollients. In more severe cases, topical steroids (1% hydrocortisone) can be used, or an oral antibiotic, such as doxycycline or minocycline, prescribed. Consider referral for a dermatology opinion if these measures are not successful.

Phototoxicity

Particularly an issue for vandetanib. Patients should be advised to avoid sun exposure by wearing protective clothing and using a high factor sun cream when outdoors. If a photosensitive rash does occur, emollients should be used in the first instance. Antihistamines can help when the rash is itchy and topical or oral steroids can be considered in

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severe cases. In such cases, treatment should be interrupted until the rash has resolved to grade 1 or less.

Weight Loss

Can be a significant problem and can contribute to fatigue. Recommend small frequent meals, consider nutritional supplements and a dietetic review. Ensure optimal management of diarrhoea and prescribe an anti-emetic if nausea is an issue.

Treatment Interruptions to Receive Other Treatments

As these agents can cause problems with wound healing, discontinuation prior to surgery or other interventional procedures (such as dental extraction) is usually recommended. The drug can be restarted once wounds have healed. The timing of discontinuation prior to surgery will depend on the half-life of the specific agent. Please see Supplementary Materials on individual drugs for specific advice.

In general, palliative radiotherapy can be given without the need for dose interruption, although this may be considered if larger fields are to be treated and there is concern about overlapping toxicity.

Treatment Beyond Progression

Once there is clear evidence of progressive disease despite treatment, the treatment should be stopped. There may be cases where progression is limited to a single site that would be amenable to local therapy. If the disease elsewhere is still controlled, it may be appropriate to continue systemic therapy.

Anaplastic Thyroid Cancer

Introduction

Anaplastic thyroid cancer (ATC) is a rare but very aggressive form of thyroid cancer. It is more common in the elderly and has an incidence of 1–2 per million population per annum [16]. Historically, outcomes have been extremely poor, with a median survival of 4–5 months [17,18], most patients presenting with advanced inoperable disease. BRAF V600E mutations are found in 20–50% of cases [19]. The development of specific inhibitors of the MAP kinase signalling pathway, in particular BRAF and MEK inhibitors, has opened up new treatment opportunities for fitter patients whose cancers carry this mutation. Options for patients without BRAF mutations are more limited, but molecular analysis is warranted as occasionally NTRK or RET fusions are identified that can be targeted with specific therapies. Other treatments, including anti-angiogenic agents and immunotherapy, are being tested in ongoing clinical trials.

BRAF V600E Mutant

A study of 100 patients with BRAF V600E mutated rare cancers treated with dabrafenib and trametinib included 16 patients with ATC [20]. An overall response rate of 69% was demonstrated in the ATC cohort. The median duration of response, progression-free survival and overall survival could not be assessed as responses were ongoing at the time of data cut-off, but Kaplan–Meier estimates at 12 months were 90%, 79% and 80%, respectively.

Responses were reported early in the course of treatment, typically within the first few weeks.

Adverse events were assessed across the entire study population. Events of grade $\geq$3 were seen in 42% of patients. Dose reduction, dose interruption and permanent discontinuation was seen in 30%, 38% and 8%, respectively.

Further evidence for the efficacy of dabrafenib and trametinib was demonstrated in a series of six patients who received the combination prior to surgery [21]. All six patients had complete resection of the thyroid tumour, and the resected specimens showed significant pathological response with a reduction in ATC viability.

BRAF V600E Wild Type

Systemic therapy options for patients without a BRAF V600E mutation are currently limited [22,23].

Cytotoxic Chemotherapy

In combination with radiotherapy regimens:

- cisplatin
- paclitaxel/carboplatin
- docetaxel/doxorubicin
- paclitaxel
- docetaxel

Chemotherapy alone:

- paclitaxel
- doxorubicin
- epirubicin
- doxorubicin and cisplatin
- paclitaxel and carboplatin

Other Targeted Therapies

In the absence of BRAF V600E mutations, molecular testing may identify other gene alterations that are targetable. This area is still under investigation and the subject of clinical trials, and at this time the following drugs have not been approved for use in the UK for this indication. Examples include tumours with NTRK, RET and ALK fusions (larotrectinib, entrectinib, selpercatinib, pralsetinib, crizotinib).

Other options being investigated include anti-angiogenic drugs (lenvatinib), immunotherapy (PD-L1 inhibitors) and

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mTOR inhibitors. Again, these drugs are not currently approved for use in the UK for this indication.

Author Contributions

All authors contributed equally to the concept of these guidelines, review of the literature and drafting, revising and approving the manuscript.

Conflicts of Interest

J. Wadsley reports a relationship with Eisai Inc that includes: consulting or advisory and speaking and lecture fees. J. Wadsley reports a relationship with Eli Lilly and Company that includes: consulting or advisory and speaking and lecture fees. J. Wadsley reports a relationship with Roche that includes: consulting or advisory and speaking and lecture fees. J. Wadsley reports a relationship with Bayer AG that includes: consulting or advisory and speaking and lecture fees. J. Wadsley reports a relationship with Ipsen that includes: consulting or advisory and speaking and lecture fees. J. Wadsley reports a relationship with Novartis that includes: consulting or advisory and speaking and lecture fees. K. Garcez reports a relationship with Eisai Inc that includes: consulting or advisory and speaking and lecture fees. K. Garcez reports a relationship with Bayer AG that includes: consulting or advisory and speaking and lecture fees. K. Garcez reports a relationship with Ipsen that includes: consulting or advisory and speaking and lecture fees.

Acknowledgement

The authors wish to acknowledge the support of Dr Laura Moss in the preparation of this manuscript, and in particular the development of the patient information leaflet, and of Mr Saul Baxter who reviewed and provided comment on the patient information leaflet.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2022.10.009.

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Please cite this article as: Wadsley J et al., Guidelines on the Use of Systemic Therapy in Patients with Advanced Thyroid Cancer, Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.009