
Article:
Carter, T.J. orcid.org/0000-0001-5940-0146, Broadfoot, J., Coupland, S.E. orcid.org/0000-0002-1464-2069 et al. (18 more authors) (2025) Uveal melanoma UK national guidelines: 2023 update. European Journal of Cancer, 228. 115687. ISSN: 0959-8049

https://doi.org/10.1016/j.ejca.2025.115687

European Journal of Cancer 228 (2025) 115687

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Review

Uveal Melanoma UK national guidelines: 2023 update

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ARTICLE INFO

Keywords:
Melanoma
Guidelines
Uveal
Choroidal
UM
UK

ABSTRACT

UK Guidelines for the management of uveal melanoma (UM) were first published in 2015 using an evidence-based systematic approach. The primary aim of this guideline was to optimise patient care by providing recommendations based on the best available scientific evidence. The resulting guideline reflected the strengths and weaknesses of the available evidence, made recommendations that were clinically impactful around prognostication, surveillance, and treatment for patients with primary lesions and metastatic disease. The guideline development process and content met the standards required by NICE and were ultimately NICE accredited. Here, we present an update to these guidelines, highlighting where practice or treatment has changed to such an extent that the original recommendations are now out of date. Presented here are updated guidelines on molecular and genetic testing, management of metastatic disease and clinical surveillance.

1. Introduction

1.1. Aim of the updated guidelines

The Melanoma Focus guideline for Uveal Melanoma (UM) was initiated in 2012 and published in 2015 [1]. The guidelines were intended to be reviewed in a five-year cycle, a process which began in 2020 and was completed in 2022. The aim of this review cycle was to identify any areas of emerging evidence, published between 2014 and September 2021, that improve or change the existing guidance. Areas where improvements in evidence, or a suggested need for guidance, were noticeable were;

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https://doi.org/10.1016/j.ejca.2025.115687
Received 11 June 2025; Received in revised form 22 July 2025; Accepted 28 July 2025
Available online 5 August 2025

I. Understanding of the genetic and molecular changes seen in uveal melanoma;
II. The role and efficacy of the currently available systemic treatment options for advanced disease and loco-regional therapies for hepatic disease;
III. The role of adjuvant radiotherapy to the orbit in cases at high-risk of local tumour recurrence and the use of palliative radiotherapy to manage advanced disease;
IV. Clinical and radiological surveillance of patients at high risk for metastatic disease.

In view of these changes, this updated summary will focus on the new guidance in these areas. In line with the original guidelines, where there is insufficient or inadequate evidence to provide guidance, consensus statements are provided by the guideline development group (GDG) to aid clinical decision making. During the process of this review cycle, no significant changes were identified in the evidence which instructs management of the primary tumour, resulting in no changes in the guidance surrounding this.

1.2. Background

UM is a rare cancer, affecting between 2 and 8 people per million per year in Caucasian populations [2–4], and rarer still in ethnic groups or peoples with brown eyes [5,6]. Most cases (>90 %) involve the choroid, with the remainder involving the iris and/or ciliary body. Some studies suggest a slight male preponderance and presentation peaks at approximately 60 years of age [7,8]. Iris melanomas usually present at a younger age [4,8,9] and < 1 % of all UM present in patients < 18 years [10–12].

The most common risk factor for developing UM is a uveal naevus, with around 10 % of cases developing from a known naevus [13]. Other risk factors are light-coloured irides, congenital ocular melanocytosis, melanocytoma, and neurofibromatosis [3,4,14–17]. The role of sunlight is uncertain [18], although recent evidence suggests that some iris melanomas have an ultraviolet radiation (UVR)-induced signature [19–21]. Familial cases of UM are very rare but include familial atypical mole and melanoma (FAMM) syndrome [22], pathogenic variants of the Breast- Cancer-Associated-1 [BRCA1]-Associated Protein 1 (BAP1) gene on chromosome 3 (BAP1-predisposition syndrome) [23,24], or BRCA2, with has been rarely associated with UM [25].

Staging for UM follows the American Joint Committee on Cancer (AJCC)/ Tumour-Node-Metastasis (TNM) staging system for eye cancer [26–29]. Outcomes vary widely, but for patients with very small tumours are excellent, if treated early [26,30]. The Liverpool Uveal Melanoma Prognosticator Online (LUMPO), is a freely available online tool which generates an all-cause mortality curve according to age, sex, AJCC TNM size category (based on basal tumour diameter and tumour height), ciliary body involvement, melanoma cytomorphology, closed loops, mitotic count, chromosome 3 loss, chromosome 8q gain, and presence of extraocular spread [31]. LUMPO3 has been externally validated by ocular oncology centres in the US and across Europe [32,33].

Over the last decade significant advances have been made in the understanding of primary UM genetics and biology, with some progress also in that of metastatic disease. In contrast to skin melanomas, posterior UM rarely exhibit mutations in BRAF and demonstrate a low mutational burden [34,35]. Instead, ~85 % of them demonstrate mutually exclusive mutations in either GNAQ (guanine nucleotide-binding protein G(q) subunit alpha q) or GNA11 (Guanine nucleotide-binding protein subunit alpha-11) [36,37]. These oncogenic mutations do not appear to be of prognostic value [38,39], but are useful for diagnostic confirmation of UM (and exclusion of most cases of cutaneous melanoma) in patients presenting with metastatic disease. Rarer initiating mutations in UM include CYSLTR2 (Cysteinyl Leukotriene Receptor 2) and PLCB4 (Phospholipase C Beta 4) [40–42]. Additional cytogenetic and genetic changes, including monosomy 3, mutations in the *BAP1* tumour suppressor gene, alterations in the splicing factors *SRSF2* (Serine and Arginine Rich Splicing Factor 2)/*SF3B1* (spliceosome factor 3b1), and mutations in the translation initiation factor *EIF1AX* (Eukaryotic Translation Initiation Factor 1A X-Linked), appear to modify the risk of metastases [34,35,43,44]. Chromosome 3 loss is associated with a reduction in 5-year survival probability from approximately 100 % to around 50 %. Similarly, chromosome 8 gains and loss of chromosome 1 also significantly correlate with reduced survival [34,35,45–49]. Conversely, gains in chromosome 6p mainly correlate with a good prognosis, suggesting this aberration may have a functionally protective effect [34,35,50,51].

The natural history of UM is characterised by the frequent development of hepatic metastases and patients may develop metastatic disease at any time from initial diagnosis of the primary to many years later [52–55]. The risk of metastatic relapse for an individual varies greatly depending on primary tumour site and morphological characteristics, as well as the presence of the genetic alterations described above [4,31,56]. Of note, most UM metastases arise from choroidal and/or ciliochoroidal melanomas. In cases of iris melanoma, dissemination of nodular well-circumscribed iridal melanomas is very rare, whilst diffuse iris melanomas are more likely to metastasise.

Imaging surveillance for the development of liver metastases can diagnose asymptomatic hepatic disease earlier, and aid the choice of treatments including surgery, liver-directed therapy and systemic therapy. The overall aim of any hepatic surveillance programme would be to detect the greatest number of relapses within a given time, accepting that it is not possible to detect all relapses in all patients. The risk of repeated radiation exposure must also be considered, particularly in a group of patients many of whom will not relapse with metastatic disease, and therefore non-ionising imaging modalities (MRI/ultrasound) are preferred. A cost-effectiveness analysis of different imaging modalities has not been performed as cost is outside the scope of this guidance.

Outcomes for patients who develop disseminated metastatic UM remain poor [57–59]. The median overall survival (mOS) from the time of the development of distant metastatic disease varies between 2 and 12 months [4], depending on several prognostic factors including disease burden and the effectiveness of metastatic screening programmes in picking up early disease [60,61]. Recent clinical trials using novel therapies do offer promise, albeit conservative optimism, in improving patient outcomes [57–59,62,63]. The liver is the most common site for UM metastases, with 50 % of patients having liver-only disease, and 90 % of those with metastases elsewhere (bowel, bone, lung and lymph nodes) also having liver metastases [4,64,65]. Liver involvement is the cause of death in most patients with metastatic UM [65], with most patients dying from parenchymal liver failure. Whilst liver disease is usually multifocal, some patients may develop isolated discrete and circumscribed metastases, enabling surgical removal. Although understanding of the underlying biology and genomics of metastatic UM has increased over the last 5 years, it remains inferior to that of primary tumours, due in part to the rarity of metastatic UM samples. However, collaborative studies have enabled improved understanding of the morphological, genetic and immunological features of these tumours [35,66–74].

1.3. Strengths and limitations of the evidence

Historically, both clinical and pre-clinical research on UM has been impeded by the rarity of the disease. Over the last 5 years, efforts by scientists and clinical teams with a specialist interest in UM has resulted in several high-quality publications including randomised controlled trials. The evidence generated from these publications has been appraised in the updated guidelines and is summarised in this manuscript.

2. Methods

These updated guidelines were assembled by Melanoma Focus, a UK national charity with professional core membership undertaking patient support in addition to research and education around melanoma and skin cancers. The guideline development group (GDG) were selected to represent centres around the UK who specialise in the primary treatment of UM, or in the treatment of patients with metastatic disease. GDG members included healthcare professionals from specialities involved in the treatment of UM including ophthalmologists, pathologists, radiologists, clinical and medical oncologists in addition to a scientist, nurse specialist, patient representatives and a project manager.

A systematic search of the literature was undertaken and reviewed by the chairman to identify guidance areas that required updating. Searches were carried out by the Royal College of Physicians National Guidelines Centre (NGC) together with initial sifting of the literature for duplicates and items that did not fit the specification. The first search took place in July 2019 covering publications from 2014 (the date of the last search) up to July 2019. An updated search was carried out 1 year later because of the delay in progress of the guideline due to the COVID-19 pandemic outbreak. A final search was carried in September 2021. The members of the 2015 development group were contacted in November 2019 asking for their opinion on which areas should be updated and inviting them to apply to be on the new development group. The first meeting of the group was held in March 2020 at the British Association of Dermatologists headquarters in London. There was then a six-month delay, due to the COVID-19 pandemic. The second meeting was held as a video-conference in October 2020. There were eight further video meetings held. The main area where it was agreed that there were no significant changes in the evidence or practice was in the management of the primary UM, therefore no evidence reviews were undertaken, and recommendations were not updated in light of new evidence.

During the initial guideline update, it became apparent that clear guidance around surveillance was also lacking. As surveillance was not included in the initial scope, it was agreed that this would be a separate piece of work and integrated into the full published guidance later. A separate GDG was created, including two patient representatives and a nurse representative from Ocular Melanoma UK. The first surveillance GDG meeting was held in September 2022. The surveillance GDG met six times in total, and the final surveillance guidelines were completed in November 2023.

2.1. Levels of evidence

Grading of evidence is based upon the Scottish Intercollegiate Guidelines Network (SIGN) grading system, last updated in 2019 (https://www.sign.ac.uk/our-guidelines/sign-50-a-guideline-developers-handbook/):

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

2.2. Grade of recommendations

Grading of recommendations is also based on SIGN 1999–2012:

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++.
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+.
GPP	Recommended best practice based on the clinical experience of the guideline development group.

3. Recommendations

3.1. Patient information and support

Receiving a diagnosis of UM can be both devastating as well as life-changing for patients and their families. Depression and anxiety are common following diagnosis, but adequate support and information can help alleviate these. In order to establish recommendations around patient information and support, a survey of patients with UM was conducted alongside a literature review of the existing clinical evidence on patient quality of life, social and emotional functioning, worries around recurrence of disease and the impact of various treatments. The reviewed literature included two systematic reviews [75,76], together with 2 cross-sectional studies and 8 cohort studies/case series [77–85].

Recommendations:

- Patients should be offered information related to their diagnosis in an individualised manner, which should adhere to appropriate quality standards, including being signposted to approved high-quality resources. **Grade: GPP**
- Patients should be given both the time and opportunity to discuss their diagnosis and the treatments they are being offered at each visit. If patients wish to record their consultation, this should be done with the knowledge of the clinician. Discussions should include: the risks and benefits of investigations, procedures and treatments; the treatments available both locally and in other centres; the advantages and disadvantages of prognostication and the role of a biopsy; information around the role of other clinical teams in their management. **Grade: GPP**
- All UM patients should have a named keyworker, who should ideally be a clinical nurse specialist. Patients should be provided with their keyworkers contact information (telephone number, e-mail address) and receive an explanation on the role of their keyworker. **Grade: GPP**
- Scan results should be given to patients as early as possible to minimise the anxiety associated with waiting for these results. **Grade: GPP**
- As a minimum, all patients at every centre should be offered;
  - o Information on the side effects of available treatments (for localised or metastatic disease)
  - o Advice regarding the signs and symptoms which may indicate disease recurrence/relapse
  - o Psychological support
  - o Easy access to clinic appointments (both in-person and remote) and the opportunity to bring a family member to appointments.
  - o An offer of early referral to services such as palliative care and support groups, if indicated.
  - o **Grade: GPP**

3.2. Genetic and molecular features

Several parameters associated with primary UM have been identified which have prognostic significance in predicting metastatic disease and therefore patient survival, roughly grouped into clinical, histomorphological, immunohistochemical, genetic and serological features. Some of these parameters are now included in the 8th AJCC TNM staging for UM [86]. As part of the updated guidelines, these prognostic parameters were reviewed to address whether new knowledge of the underlying genetics of UM has influenced the design of prognostic tools and whether these can therefore better define metastatic risk. In addition, the relative advantages and disadvantages of undertaking a prognostic UM biopsy were summarised, to facilitate discussion with patients around the requirement for this in their case (Table 1).

Recommendations (those updated from the 2015 guidelines are marked [2022]):

- The following prognostic features should be recorded for each patient: Age, sex, tumour location, tumour height, tumour largest basal diameter, ciliary body involvement, extraocular spread (micro- and macroscopic). **Grade: A**
- If tissue is available, the following features should also be recorded:
  - Cell type (modified Callender system)
  - Mitotic count (number/high power fields (or mm^2) in H&E-stained sections)
  - Presence of extravascular matrix patterns (in particular – closed loops) (Grade A)
  - Presence of extraocular melanoma growth (size in mm [<5 mm or >5 mm], presence/absence of encapsulation, relation to surgical margin)
  - Positive or negative expression of nuclear BAP1 protein in the tumour cells [2022].
  - **Grade: A**
- If cytology of tumour is available [2022]:
  - Confirmation of melanoma cells (exclusion of metastatic carcinoma) and immunocytology
  - Cell type (modified Callender system – if possible)
  - Positive or negative expression of BAP1 protein, if possible
  - **Grade: A**
- A fully informed discussion should take place with all patients on the role of biopsy (Table 1). Discussion should cover:
  - Prognostication and tailored follow-up
  - Recruitment into adjuvant trials
  - Risks and benefits of the biopsy
  - Limitations of the biopsy
  - Impact of prognostication of QoL [2022]
  - **Grade: GPP**

Table 1
Advantages and disadvantages of undertaking a UM biopsy.

Advantages	Disadvantages
Confirmation of diagnosis in very small melanomas (differential diagnosis, naevus)	Currently no influence on treatment of metastatic disease
Psychological impact – 'forewarned is forearmed'	Low potential of vision threatening complications
Justifying screening examination in patients with small tumours and high-risk characteristics	Small risk of tumour cell seeding
Possible screening exclusions of patients with low-risk characteristics	Possibility of 'negative' biopsies (5–10 % cases, more common in small or necrotic tumours)
Inclusion into future trials of adjuvant treatment to prevent metastatic disease	Test results not 100 % predictive when 'standalone' – needs incorporation with other prognostic parameters
Influence on treatment in selected cases	Psychological impact: high-risk result can be devastating for some patients, and they will need support.

- Minimum dataset for UM as per the Royal College of Pathology should be recorded for all patients (https://www.rcpath.org/profession/publications/cancer-datasets.html). [2022] **Grade: GPP**
- The most up-to-date edition of TNM staging should be used for prognostication and included in pathology/clinical reports. [2022] **Grade: GPP**
- Provided patient consent has been obtained as part of an ethically approved research programme, molecular genetic and/or cytogenetic data should be collected where available for research and prognostication purposes. [2022] **Grade: GPP**
- Use of multifactorial prognostication models that incorporate clinical, histological, immunohistochemical and genetic tumour features should be considered. [2022] **Grade: GPP**
- Where available, results of molecular analysis should be combined with clinical features and standard anatomical/pathological staging for prognostication. [2022] **Grade: GPP**
- Tests for novel circulating blood-borne biomarkers should only be used within clinical trials or research programmes. [2022] **Grade: GPP**

3.3. Adjuvant therapy

3.3.1. Adjuvant systemic therapy

Given that around half of all patients diagnosed with UM will develop metastatic disease, that there remainlimited treatment options for metastatic UM, and indeed any treatment available is not delivered with curative intent, an effective adjuvant treatment would significantly impact long-term survival outcomes in UM. Due to a lack of clinical trials, adjuvant therapy was not addressed in the 2015 guideline. An updated literature search identified eleven clinical studies reporting on adjuvant therapy which form the evidence base for these recommendations (Table 2). Several studies investigating adjuvant systemic therapies in UM were ongoing at the time of guideline review, and therefore could not be considered.

Evidence Statements:

- There is currently insufficient evidence to support the use of adjuvant systemic therapy outside of clinical trials.
- Whilst some single arm studies have shown a potential signal for benefit, these require validation in larger, randomised studies, or comparison with well-matched controls.
- The availability of well validated prognostic markers that correlate strongly with survival, provide a means to identify patients who would benefit from active adjuvant agents and further trials in this area are urgently needed.

Recommendations:

- The availability of prognostic tools to identify high-risk primary disease support ongoing exploration into adjuvant approaches for UM. **Grade: GPP**
- In the absence of proven therapy, adjuvant systemic therapy should only be given within a well-designed clinical trial. **Grade: GPP**

3.3.2. Adjuvant radiation therapy

Extra-ocular extension occurs in 2–6 % of patients with UM, and up to 13 % of those undergoing enucleation. The presence of extra-ocular extension is associated with increased risk of both local recurrence and metastatic spread. There is a lack of data as to whether external beam radiation therapy to the orbit after enucleation confers a survival benefit or reduces the risk of a local relapse. Furthermore, radiation therapy is associated with toxicities including socket contracture and wound breakdown. To date, there are no randomised controlled trials comparing radiation against observation for patients following enucleation for UM. Two observational studies form the backbone of the clinical evidence available to date on adjuvant radiotherapy in UM (Table 3) [98,99].

Recommendations:

Table 2
Summary of key adjuvant systemic therapy studies.

Author & Reference	Year	Study Type	Title
McLean [87]	1990	Randomised Study	A randomised study of methanol-extraction residue of bacilli Calmette-Guerin as postsurgical adjuvant therapy of uveal melanoma
Desjardins [88]	1998	Randomised Study	Randomised study of adjuvant therapy by DTIC in choroidal melanoma
Voelter [89]	2008	Case Series	Adjuvant intra-arterial hepatic fotemustine for high-risk uveal melanoma patients
Lane [90]	2009	Single Arm Study	Adjuvant interferon Therapy for Patients with Uveal Melanoma at high-risk of metastasis
Lawson [91]	2015	Randomised Phase III Study	Randomised, placebo controlled, phase III trial of yeast-derived granulocyte-macrophage colony stimulating factor (GM-CSF) versus peptide vaccination versus GM-CSF plus peptide vaccination in patients with no evidence of disease after comp
Piperno-Neumann [92]	2017	Randomised Phase III Study	A randomised multicentre phase 3 trial of adjuvant fotemustine versus surveillance in high-risk uveal melanoma (UM) patients (FOTEADJ)
Mao [93]	2017	Non-Randomised Retrospective Cohort Analysis	Choice of adjuvant therapy in uveal melanoma: A retrospective analysis in China
Valsecchi [94]	2018	Non-randomised	Adjuvant Sunitinib in High-Risk Patients with Uveal Melanoma: Comparison with Institutional Controls
Fountain [95]	2019	Non-randomised Study	Adjuvant Ipilimumab in High-Risk Uveal Melanoma
Binkley [96]	2020	Non-randomised Study	A prospective trial of adjuvant therapy for high-risk uveal melanoma: assessing 5-year survival outcomes
Sato [97]	2020	Randomised Non-Comparative Study	A randomised phase II study of adjuvant sunitinib or valproic acid in high-risk patients with uveal melanoma

Table 3
Clinical Studies of adjuvant radiation therapy.

Author & Reference	Year	Study Type	Title
Hykin[98]	1990	Observational Study	Post-enucleation orbital radiotherapy for the treatment of malignant melanoma of the choroid with Extrascleral Extension
Roelofs[99]	2020	Observational Study	Adjuvant External Beam Radiotherapy Following Enucleation of Eyes with Extraocular Extension

- There is very limited evidence for adjuvant radiation therapy to the orbit after definitive surgical treatment of primary disease. It is an option that can be considered for patients deemed to be at high risk of local relapse (e.g. greater than 5 mm of extra-ocular extension). The risks of toxicity should be balanced against the lack of evidence for efficacy, with patients counselled appropriately. **Grade: D**
- When radiation therapy is indicated, due to the relative radio-resistance of melanoma, doses greater than 2 Gy per fraction are recommended with a total dose of 45–50Gy/20#. **Grade: C**

3.4. Treatment options for macroscopic orbital recurrence

To date, there is no evidence-based consensus on the treatment of orbital recurrence, and as such treatment is decided on a case-by-case basis.

Recommendations:

- Patients who present with macroscopic orbital recurrence should be discussed at a multidisciplinary meeting to discuss both surgical and radiation treatment options. **Grade: GPP**
- When radiation therapy is indicated, due to the relative radio-resistance of melanoma, doses greater than 2 Gy per fraction are recommended with a total dose of 45–50Gy/20#. **Grade: GPP**

3.5. Metastatic disease

3.5.1. Systemic treatment

The optimal systemic management of metastatic UM remains an area of unmet need. At the time of publication of the original guidelines in 2015, randomised controlled trial (RCT) evidence in metastatic UM was limited. Since this, several clinical studies have been published or presented, including 12 randomised trials and 19 non-randomised trials. The key studies which formed the evidence base for the updated 2022 recommendations are summarised in Table 4.

Evidence Statements:

- There is no robust evidence supporting a survival improvement with cytotoxic chemotherapy. **Grade: B**
- Studies investigating MEK inhibitors either as monotherapy or in combination with other agents demonstrate low activity rates in metastatic UM. **Grade: A**
- Similarly, targeted agents such as sunitinib, cabozantinib and sorafenib have not demonstrated clinical efficacy in clinical trials. **Grade: B**
- Response rates to immune checkpoint inhibitors are low; ~5 % for single agent treatment, and 12–18 % for combination. Clinical benefit rate may be higher. **Grade: B**
- Although immune checkpoint inhibitors are used as standard of care in contemporary clinical trials, their activity has never been compared to placebo or no treatment. **Grade: B**
- Adoptive T cell therapy has shown activity in a single phase II trial, but randomised or confirmatory data are not available. **Grade: D**
- Tebentafusp has demonstrated improved survival in the first line setting in a randomised phase III study (compared to investigator choice), as well as prolonged survival in a separate single arm study in the second line, when compared to historic controls. **Grade: A**
- Tebentafusp only has activity in patients with HLA-A*02:01 genotype. **Grade: A**

Recommendations:

- Consider offering tebentafusp to HLA-A*A02:01 positive patients with metastatic disease who possess sufficient ECOG performance status. **Grade: A**

3.5.2 Loco-regional management of hepatic predominant metastatic disease

The liver is the most common site for metastatic spread in patients with systemic relapse of UM. Up to 85 % of patients with metastatic disease will develop hepatic metastases, and for around 50 % of patients, the liver is the sole site of relapse (REF). This provides a rationale for the therapeutic targeting of a single organ. Treatment approaches include surgical and ablation therapy, chemosaturation either via percutaneous hepatic perfusion (PHP) or hepatic artery infusion (HAI), radio-embolisation (SIRT) and chemo-embolisation (TACE). The key clinical studies utilised in the production of these updated guidelines for the management of hepatic-predominant or oligo-metastatic disease are summarised in Table 5. Comparing the efficacy of these different

Table 4
Systemic therapy for metastatic disease.

Author & Reference	Year	Title
Multi-Agent Studies		
Itchens[100]	2017	A multireferral centre retrospective cohort analysis on the experience in treatment of metastatic uveal melanoma and utilization of sequential liver-directed treatment and immunotherapy
Jochems[101]	2019	Metastatic Uveal Melanoma: Treatment Strategies and Survival-Results from the Dutch Melanoma Treatment Registry
Khoja[102]	2019	Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study
Lane[103]	2018	Survival rates in patients after treatment for metastasis from uveal melanoma
Moser[104]	2015	The Mayo Clinic experience with the use of kinase inhibitors, ipilimumab, bevacizumab, and local therapies in the treatment of metastatic uveal melanoma
Nicholas[105]	2018	Prognostic factors for first-line therapy and overall survival of metastatic uveal melanoma: The Princess Margaret Cancer Centre experience
Rantala[106]	2019	Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis
Rodriguez-Vidal [107]	2021	Treatment of Metastatic Uveal Melanoma: Systematic Review
Seedor[108]	2020	An Outcome Assessment of a Single Institution's Longitudinal Experience with Uveal Melanoma Patients with Liver Metastasis
Chemotherapy		
Lee[109]	2015	Results of a Phase II Study to Evaluate the Efficacy of Docetaxel and Carboplatin in Metastatic Malignant Melanoma Patients Who Failed First-Line Therapy Containing Dacarbazine
Peuker[110]	2018	Retrospective analysis of the treatment of metastatic uveal melanoma comparing systemic chemotherapy and transarterial chemoembolization
Schinzari[111]	2017	Cisplatin, dacarbazine and vinblastine as first line chemotherapy for liver metastatic uveal melanoma in the era of immunotherapy: a single institution phase II study
Targeted Treatment		
Caravajal[112]	2014	Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial
Luke[113]	2020	Randomized Phase II Trial and Tumor Mutational Spectrum Analysis from Cabozantinib versus Chemotherapy in Metastatic Uveal Melanoma (Alliance A091201)
Nathan[114]	2019	SELPAC: a 3 arm randomised phase II study of the MEK inhibitor selumetinib alone or in combination with paclitaxel (PT) in metastatic uveal melanoma (UM)
Piperno-Neumann[115]	2020	Genomic Profiling of Metastatic Uveal Melanoma and Clinical Results of a Phase I Study of the Protein Kinase C Inhibitor AEB071.
Steeb [116]	2018	How to MEK the best of uveal melanoma: A systematic review on the efficacy and safety of MEK inhibitors in metastatic or unresectable uveal melanoma.
Sacco [117]	2013	Sunitinib versus dacarbazine as first-line treatment in patients with metastatic uveal melanoma
Scheulen [118]	2017	STREAM: a randomized discontinuation, blinded, placebo-controlled phase II study of sorafenib (S) treatment of chemonaïve patients (pts) with metastatic uveal melanoma (MUM)
Immune Checkpoint Inhibitors		
Heppt [119]	2017	Immune checkpoint blockade for unresectable or metastatic uveal melanoma: A systematic review
Kottschade[120]	2016	The use of pembrolizumab for the treatment of metastatic uveal melanoma
Mignard[121]	2018	Efficacy of Immunotherapy in patients with metastatic mucosal or uveal melanoma
Nathan [122]	2019	Safety and efficacy of nivolumab in patients with rare melanoma subtypes who progressed on or after ipilimumab treatment: a single-arm, open-label, phase II study (CheckMate 172)
Heppt[123]	2017	Prognostic factors and outcomes in metastatic uveal melanoma treated with programmed cell death−1 or combined PD−1.CTLA−4 inhibition
Koch [61]	2021	Immune Checkpoint Blockade for Metastatic Uveal Melanoma: Patterns of Response and Survival According to the Presence of Hepatic and Extrahepatic Metastasis
Najjar[124]	2020	Ipilimumab plus nivolumab for patients with metastatic uveal melanoma: a multicenter, retrospective study
Pelster[125]	2021	Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study
Piulats[126]	2021	Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM−1402)
Zimmer[127]	2015	Phase II DeCOG-study of ipilimumab in pretreated and treatment-naive patients with metastatic uveal melanoma
Tebentafusp		
Piperno-Neumann[128]	2021	Phase 3 randomised trial comparing tebentafusp with investigator's choice in first-line metastatic uveal melanoma
Nathan [63]	2021	Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med [Internet]. 2021 Sep 23 [cited 2021 Dec 7];385 (13):1196–206.
Sacco [129]	2020	A Phase 2 multi-centre study of the safety and efficacy of tebentafusp in patients with metastatic uveal melanoma (IMCgp100–102)

treatment modalities was challenging given the range of inclusion criteria within the studies, and the time points at which focal treatment was offered in relation to systemic therapies. There was no obvious advantage found to any one approach over another, although PHP and SIRT were found to have the longest OS outcomes of all the liver directed therapies.

Evidence Statements:

- Liver resection with the aim of macroscopic clearance may be associated with longer survival in selected patients, compared with patients who do not undergo surgery.
- There is no evidence to support hepatic debulking surgery. **Grade: D**
- Regional liver-directed treatments (PHP/IHP, SIRT, TACE) can reduce measurable tumour burden. Whilst there is a sparsity of randomised data, outcomes may be improved in selective patients when compared with historic controls. **Grade: B**

Recommendations:

- Assessment for hepatic resection should be offered when complete (R0) resection can be achieved. Early interval imaging is helpful to exclude patients with rapidly progressing disease. Patient selection for surgery should take the following into account:
  - o The extent of liver involvement
  - o The absence of presence of extra-hepatic disease (ideally no more than one extra-hepatic site, which is either stable, or with an alternative treatment strategy).
  - o ECOG PS 0–1
  - o Functionally significant volume of liver disease to justify the surgery
  - o **Grade: GPP**
- For patients offered surgery, laparoscopic assessment should be performed beforehand to identify any patients with miliary disease not visible on imaging; a pattern of disease common amongst patients with metastatic UM. **Grade: GPP**
- Liver-directed or systemic treatments should be considered in selected patients with liver predominant disease where resection is not possible. **Grade: GPP**
- Post-treatment of liver metastases, patients should be offered imaging surveillance with regular imaging of the chest, abdomen and

Table 5
Loco-regional Management of Liver Metastases.

Author & Reference	Year	Title
Artzner[130]	2019	Chemosaturation with percutaneous hepatic perfusion of melphalan for liver-dominant metastatic uveal melanoma: a single center experience.
Broman[131]	2019	Intra-arterial perfusion-based therapies for regionally metastatic cutaneous and uveal melanoma.
Carling[131]	2015	Transarterial Chemoembolization of Liver Metastases from Uveal Melanoma Using Irinotecan-Loaded Beads: Treatment Response and Complications.
Eichler[132]	2014	MR-guided laser induced thermotherapy (LITT) in patients with liver metastases of uveal melanoma.
Eldredge-Hindy [133]	2016	Yttrium−90 microsphere brachytherapy for liver metastases from uvealmelanoma: clinical outcomes and the predictive value of fluorodeoxyglucose positron emission tomography.
Gomez[134]	2014	The Liverpool Uveal Melanoma Liver Metastases Pathway: Outcome following liver resection.
Gonsalves[135]	2019	A Prospective Phase II Trial of Radioembolization for Treatment of Uveal Melanoma Hepatic Metastasis.
Gonsalves[136]	2015	Uveal Melanoma Metastatic to the Liver: Chemoembolization With 1,3-Bis- (2-Chloroethyl)−1-Nitrosourea.
Hand[137]	2020	Metastatic uveal melanoma: A valid indication for liver resection.
Karydis[138]	2016	Clinical activity and safety of Pembrolizumab in Ipilimumab pre-treated patients with uveal melanoma.
Levey[139]	2020	Predictors of Overall and Progression-Free Survival in Patients with Ocular Melanoma Metastatic to the Liver Undergoing Y90 Radioembolization.
Leyvraz[140]	2014	Hepatic intra-arterial versus intravenous fotemustine in patients with liver metastases from uveal melanoma (EORTC 18021): a multicentric randomized trial.
Meijer[141]	2021	Percutaneous Hepatic Perfusion with Melphalan in Patients with Unresectable Ocular Melanoma Metastases Confined to the Liver: A Prospective Phase II Study.
Olofsson[142]	2014	Isolated hepatic perfusion for ocular melanoma metastasis: registry data suggests a survival benefit.
Reddy[143]	2014	Isolated hepatic perfusion for patients with liver metastases.
Rowcroft[144]	2020	Systematic review of liver directed therapy for uveal melanoma hepatic metastases.
Schonfeld[145]	2020	Chemosaturation with percutaneous hepatic perfusion is effective in patients with ocular melanoma and cholangiocarcinoma.
Seedor[108]	2020	An Outcome Assessment of a Single Institution's Longitudinal Experience with Uveal Melanoma Patients with Liver Metastasis.
Servois[146]	2019	Iterative treatment with surgery and radiofrequency ablation of uveal melanoma liver metastasis: Retrospective analysis of a series of very long- term survivors.
Shibayama[147]	2017	Efficacy and toxicity of transarterial chemo- embolization therapy using cisplatin and gelatin sponge in patients with liver metastases from uveal melanoma in an Asian population.
Valpione[148]	2015	A retrospective analysis of 141 patients with liver metastases from uveal melanoma: a two-cohort study comparing transarterial chemoembolization with CPT−11 charged microbeads and historical treatments.
Valsecchi[149]	2015	Double-blinded, randomized phase II study using embolization with or without granulocyte-macrophage colony-stimulating factor in uveal melanoma with hepatic metastases.
Vogl[150]	2017	Percutaneous isolated hepatic perfusion as a treatment for isolated hepatic metastases of uveal melanoma: patient outcome and safety in a multi-centre study.
White[151]	2016	Recurrence and survival outcomes after percutaneous thermal ablation of oligometastatic melanoma.
Zager[152]	2021	Percutaneous hepatic perfusion (PHP) with melphalan for patients withocular melanoma liver metastases: Preliminary results of FOCUS (PHP-OCM−301/301A) phase III trial.
Zager[153]	2012	Chemosaturation therapy with percutaneous hepatic perfusion of melphalan versus standard of care in patients with hepatic metastases from melanoma: a randomized multicenter phase 3 study.

pelvis. Frequency of imaging can be tailored to the patient and treatment modality. **Grade: GPP**
- Patient outcomes for this selected group should be collected centrally and prospectively. **Grade: GPP**

3.6. *Surveillance of patients at risk of recurrence*

3.6.1. *Ocular surveillance for tumour recurrence*

Monitoring of patients following treatment for primary UM is important for three main reasons;

1. Monitoring for recurrence
2. Monitoring for radiation-related side-effects
3. Counselling and emotional support.

Radiation-induced side effects include radiation maculopathy, radiation retinopathy, serous retinal detachment, neovascular glaucoma, cataract, optic neuropathy, vitreous haemorrhage, scleral necrosis and tantalum marker extrusion. All these complications can respond to ophthalmic treatment. A literature review was conducted to better understand the timing of recurrence or radiation related complications [154–161].

Evidence Statements:

- Most (80 %) local recurrences occur within 3 years. Rarely, recurrence can occur at a longer time after treatment.
- 98 % of recurrences are picked up via colour photography of the fundus (provided there is a clear view).
- Most complications from radiotherapy occur within 5 years of treatment.
- The risk of UM in the contralateral eye is very small except in cases of rare familial syndromes.

Recommendations:

- Patients should be offered surveillance of the affected eye every 6 months for 2–5 years, and then annually (depending on response to therapy and individual patient factors). **Grade: GPP**
  - o In cases where there is doubt over local tumour control, surveillance frequency should be increased as needed to confirm or refute stability.
  - o Surveillance can be conducted via colour photography provided there is a clear view of the whole tumour. This can be conducted locally, or at ocular oncology centres.
  - o In patients whose entire tumour cannot be visualised, surveillance can be aided with ocular ultrasound.
  - o If tumours have completely regressed, patients can be discharged to local optometry services.
  - o Patients who have had enucleation with clear margins (R0 resection) can be discharged to an ocularist once the socket is healed.
- Prior to discharge from the Ocular Oncologist, patients should have a clear plan in place for metastatic surveillance, if this is indicated – see 3.6.2. **Grade: GPP**
- Ongoing ocular surveillance, if needed, can be carried out by a general ophthalmologist or optometrist with appropriate expertise. This should be continued for life. **Grade: GPP**
  - o Patients should be copied into correspondence between Ocular Oncology and their local services with a summary of the follow up plan.
  - o If patients have not heard from the onward team within two months, they should be encouraged to contact the referring centre.

- Management of ocular morbidities may require advisory input from the Ocular Oncologist. **Grade: GPP**

3.6.2. Liver surveillance

For the 2015 guideline, there was a lack of evidence regarding who best to offer surveillance to, and whether surveillance impacted on patient outcomes. As such, these initial 2015 guidelines recommended that all patients be offered a discussion around surveillance, irrespective of risk, and those judged at high-risk should have 6 monthly life-long surveillance with a non-ionising imaging modality. In this first iteration of the guideline, high risk was not defined, therefore the 2022 guideline group reviewed the literature from 2015 onwards to address the utility of metastatic liver surveillance for UM patients.

Evidence Statements:

- There is no prospective evidence that imaging surveillance impacts on the cancer outcomes for patients with UM
- There is some evidence that patients with stage 4a disease do better than patients with stage 4b and 4c disease when treated with surgery or tebentafusp [63].
- There is indirect evidence that patients undergoing metastatic imaging surveillance may have metastases identified at a stage when more effective treatments are available

3.6.2.1. Metastatic risk determination. There are several prognostic systems available to clinicians managing patients with uveal melanoma [162]. The most widely utilised of these is 'The Liverpool Uveal Melanoma Prognosticator Online' (LUMPO) version 3: a semiparametric algorithm that can predict recurrence risk for patients diagnosed with uveal melanoma[163], which has been externally validated [164]. LUMPO3 has several strengths and weaknesses (Table 6), which must be considered when risk-scoring patients.

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3.6.2.2. Frequency of imaging and duration of surveillance. Evidence Statements:

- UM mortality is stable 10 years after diagnosis and most deaths beyond this stage are from other causes.

Table 6
Strengths and Weaknesses of LUMPO3 metastatic risk scoring.

Strengths	Weaknesses
Multiparameter UM prognostication model utilising clinical, histomorphological and genomic information	No defined cut-off to define high and low risk
Compared to age and gender-matched populationBuilt on large datasets with robust internal and external validation, therefore no longer viewed as an 'experimental tool'	Accuracy of prediction limited by number of values inputted into algorithm
Allows for continued revision and incorporation of new knowledge and parameters, with potential for use in clinical trials	Tumour genetic status is a strong predictor within LUMPO3, therefore its accuracy is less when chromosome 3 cannot be included in the algorithm Relatively large number of data inputs required (n = 9)
Infographics designed to enable good understanding by patients and families	Does not include mutational status of cells (BAP1, SF3B1, EIFAX1) TNM staging more widespread globally
Website allows for global usage (pending approval of applications for approval for use outside the UK post-Brexit)	To enable further revisions to the algorithm, large numbers of data points are needed Predicts risk at time of diagnosis but does not alter this prediction as time progresses

- A proportion of patients under the age of 60 at diagnosis are at risk of recurrence for longer.
- In patients with small primary lesions and a good prognosis (i.e. tumours possess of one of the following: a) disomy chromosome 3 (FISH), b) class 1 (GEP), c) absence of BAP1 loss or SF3B1 mutation (SS and NGS)) the risk of relapse is typically very low.
- Patients with small tumours and no cytogenetic analysis available usually have excellent outcomes. However, for patients with small tumours and monosomy 3, 23 % developed metastases, hence these patients should be considered for surveillance [30].
- Follow up of patients with SF3B1 aberrations suggest that they are at risk of a late relapse beyond 10 years.
- About 15 % of UM carry SF3B1 mutation which puts them at risk of later relapse.

3.6.2.3. Imaging modality. Ultrasound (US) and magnetic resonance imaging (MRI) are the most sensitive surveillance methods to detect hepatic metastases in patients with UM with no radiation implications. When MRI is used, non-contrast scans with diffusion weighted imaging (DWI) are preferable. Contrast enhanced MRI scans should be used when lesion characterisation is required in cases of diagnostic uncertainty, given that MRI provides better characterisation of lesions. When US is used, an MRI should be scheduled if any new lesion is detected. High risk patients may be followed with 6 monthly MRI scans for early detection of those who may benefit from liver resection.

Recommendations:

- Patients should be offered a discussion with an oncologist or other professional to discuss the relative merits of metastatic surveillance. Surveillance should be coordinated through secondary care and not primary care. **Grade: GPP**
- A multi-parameter prognostic model (e.g. LUMPO) should be utilised to calculate individual metastatic risk, and therefore the merits of liver surveillance. **Grade: B**
- For patients without genetic analyses, modelling with LUMPO to estimate risk with or without monosomy 3 may inform discussion around recurrence risk. **Grade: B**
- Patients with a recurrence risk below 10 % within a 10-year period as estimated by LUMPO (or equivalent) should not be recommended liver surveillance. **Grade: GPP**
- Patients with small tumours (T1) and favourable histological/genetic analyses (disomy chromosome 3, class 1 (GEP), absence of BAP1 loss or SF3B1 mutation) may not need imaging surveillance. **Grade: GPP**
- Any decision to start surveillance (including a decision on duration) should be individualised based on factors including comorbidities and patient fitness to act on findings. **Grade: GPP**
- Standard surveillance should be for 10 years from initial ocular diagnosis. Imaging should be every 6 months for 5 years, and then annually to 10 years. Choice of imaging modality should be discussed with patients but should be liver focussed. **Grade: GPP**
- Patients with confirmed SF3B1 mutation may benefit from extended surveillance to 15 years. **Grade: GPP**
- US and MRI are considered equally effective for decision making. Patient factors may influence choice of imaging modality. **Grade: C**
- For MR surveillance, non-contrast, DWI sequences are recommended, with contrast agents used only at baseline and when indicated to characterise new lesions. **Grade: GPP**
- US should be performed by an experienced operator. MRI should be scheduled if new lesions are identified. **Grade: GPP**
- FDG-PET-CT and CT imaging are not recommended for liver surveillance. **Grade: D**
- Liver function tests are an inadequate tool for UM surveillance and should not be part of routine surveillance. **Grade: GPP**
- All patients should have access to psychological services including those who are not offered surveillance. **Grade: GPP**

Table 7
Notable new publications since the updated guideline.

Author & Reference	Year	Title
Hassel[166]	2023	Three-Year Overall Survival with Tebentafusp in Metastatic Uveal Melanoma.
Carvajal[172]	2022	Clinical and molecular response to tebentafusp in previously treated patients with metastatic uveal melanoma: a phase 2 trial.
Carvajal[165]	2022	Phase I Study of Safety, Tolerability, and Efficacy of Tebentafusp Using a Step-Up Dosing Regimen and Expansion in Patients With Metastatic Uveal Melanoma.
Yamada[173]	2024	Immune checkpoint inhibitors for metastatic uveal melanoma: a meta-analysis.
Wu[174]	2024	Uveal melanoma distant metastasis prediction system: A retrospective observational study based on machine learning.
Piulats[175]	2024	Overall survival from tebentafusp versus nivolumab plus ipilimumab in first-line metastatic uveal melanoma: a propensity score-weighted analysis.
Zager[168]	2024	Efficacy and Safety of the Melphalan/Hepatic Delivery System in Patients with Unresectable Metastatic Uveal Melanoma: Results from an Open-Label, Single-Arm, Multicenter Phase 3 Study.
Zager[169]	2025	An open-label, randomized study of melphalan/hepatic delivery system versus best alternative care in patients with unresectable metastatic uveal melanoma
Dian[176]	2024	Efficacy and safety of tebentafusp in patients with metastatic uveal melanoma: A systematic review and meta-analysis.
Pham[177]	2023	Efficacy of immune checkpoint inhibition in metastatic uveal melanoma: a systematic review and meta-analysis.
Sacco[178]	2024	Long-term survival follow-up for tebentafusp in previously treated metastatic uveal melanoma.
Buchbinder[179]	2024	A Phase II Study of ERK Inhibition by Ulixertinib (BVD−523) in Metastatic Uveal Melanoma.
Rodrigues[180]	2024	Prospective assessment of circulating tumor DNA in patients with metastatic uveal melanoma treated with tebentafusp.
Sacco[181]	2024	A three-arm randomised phase II study of the MEK inhibitor selumetinib alone or in combination with paclitaxel in metastatic uveal melanoma.
Harbour[182]	2024	15-Gene Expression Profile and PRAME as Integrated Prognostic Test for Uveal Melanoma: First Report of Collaborative Ocular Oncology Group Study No. 2 (COOG2.1).
Du[183]	2025	Efficacy and safety of robotic Cyberknife radiotherapy in uveal melanoma: a systematic review and meta-analysis.
Singh[184]	2022	Predicted vs Observed Metastasis-Free Survival in Individuals With Uveal Melanoma.
Olofsson Bagge [167]	2023	Isolated Hepatic Perfusion With Melphalan for Patients With Isolated Uveal Melanoma Liver Metastases: A Multicenter, Randomized, Open-Label, Phase III Trial (the SCANDIUM Trial).
Vitek[185]	2024	Efficacy and Tolerability of Tebentafusp in Metastatic Uveal Melanoma: A Real-life Retrospective Multicentre Study.
Koch[186]	2023	Liver-directed treatment is associated with improved survival and increased response to immune checkpoint blockade in metastatic uveal melanoma: results from a retrospective multicenter trial.
Muller[187]	2024	Anxiety, depression and fear of cancer recurrence in uveal melanoma survivors and ophthalmologist/oncologist communication during survivorship in France - protocol of a prospective observational mixed-method study.
Tacar[188]	2021	Nivolumab for metastatic uveal melanoma: a multicenter, retrospective study.
Kosydar[189]	2021	Systematic Review and Meta-Analysis on the Use of Photon-based Stereotactic Radiosurgery Versus Fractionated Stereotactic Radiotherapy for the Treatment of Uveal Melanoma.
Delaney[171]	2025	Surveillance for Metastasis in Low-Risk Uveal Melanoma Patients: Need for Optimization
Chung[170]	2024	Gadoxetic acid-enhanced MRI for the detection of liver metastases from melanoma

- Patients who are discharged (to GP or ophthalmologist) following completion of surveillance, should be referred back to an oncologist if there are any concerns of late metastatic recurrence. **Grade: GPP**

Notable Published Updates Since the Updated Guideline

The updated guideline was finalised in May 2022, with the surveillance guidelines added in November 2023. The final literature search conducted in September 2021, and the next formal review cycle is due in late 2026. In view of this, a list of notable clinical updates, published between September 2021 and March 2025, was collated which support the current guidelines (Table 7). To collate this list, a literature search was undertaken mirroring the methodology of the original guideline, with relevant publications selected by the authors. With the exception of the Phase I study which established the step-up dosing regimen for treatment with tebentafusp [165], phase I studies were excluded from this list. Updates included further clinical publications on tebentafusp, including optimum dosing schedules [165], and 3 year survival data [166]. In addition, results from both the SCANDIUM trial [167] and the FOCUS trial [168,169] were published. Finally, further articles around optimal hepatic surveillance modalities and schedules were also published [170,171]. These, and other publications in Table 7 will be considered in full within the next full guideline update.

4. Conclusion

Since 2015, there have been several developments in both the understanding of the biology of UM, stratification of risk, and treatment options for metastatic disease. Early and later phase clinical trials are ongoing in the neoadjuvant, adjuvant and metastatic setting, which may result in further changes in the standard of care treatment for patients with UM. Further guideline updates will be completed in 2027, which may reflect further developments to help patients with this rare cancer.

CRediT authorship contribution statement

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Funding

The development of the guideline was funded by Melanoma Focus (https://melanomafocus.org/) with a donation from Ocular Melanoma

UK (https://www.ocumeluk.org/). No additional funding was received for the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

All GDG members completed a Declaration of Interest form prior to attending their first meeting. All interests were declared at the first meeting. It was agreed that members with a commercial interest in any drug or technology under discussion could remain in the room and answer questions from GDG members but were not allowed to participate in the discussion or the formulation of recommendations.

Dr. Thomas Carter: Speaker fees from the following companies: BMS, MSD, Regeneron. Institutional grant from MSD.

Jack Broadfoot - Nil

Prof Sarah Coupland: Advisor to ImmunoCore.

Prof Bertil Damato: Immunocore Ltd. Consultant. Consultancy work for AURA and Eckert and Ziegler and Ideaya biosciences. Advisor to CureOM, Ocular Melanoma UK and A Cure in Sight.

Helen Evans - Nil

Mr Stephen Fenwick: Contributed to AdBoards run by Delcath Systems Inc, and contributed to the Medical Advisory Board of OcuMel UK

Leila Khoja – Nil

Tracey Krausa – Nil

Rachel Lewis - Nil

Dr Sachin Modi: Paid consultancy for DELCATH

Prof. Paul Nathan: Advisory board member for BMS, Immuncore, Ipsen, Merck, MSD, Novartis, Pfizer, 4SC. TSG member for Novartis & Ipsen studies. Institution has received research funding from Immunocore

Guy Negretti – Nil

Sukaina Rashid - Nil

Dr Joe Sacco: Received honoraria from BMS and Immunocore; received travel and conference expenses from BMS, MSD and Immunocore; participated in paid advisory boards for Immunocore, Delcath, MSD, Amgen and Immuncore. Institution has received research funding from AstraZeneca, BMS and Immunocore.

Dr Heather Shaw: Honoraria and fees for speaking at educational meetings, advisory board and travel expenses from BMS/MSD. Payment to department related to conduct of clinical studies – BMS, MSD, Immunocore.

Karen Sisley – Nil

Reta Sowton – Nil

Samra Turajilic – Nil

Nancy Turnbull - Nil

Dr Matthew Wheater: Speaker fees, consultancy and conference fees from the following companies: BMS, MSD, Delcath Systems. Research funding from BMS, MSD and Delcath systems.

Acknowledgements

The GDG is grateful to Melanoma Focus for its support in funding the development of this guideline and for hosting the consultations and the final products; (https://melanomafocus.org/). Financial support was provided to the initial GDG with a donation from Ocular Melanoma UK (https://omuk.org/). Thanks also to patient representative and author Audrey Woraker who passed away after production of the review.

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