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Management of metastatic uveal melanoma: French expert consensus guidelines

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Summary

Uveal melanoma (UM) is a rare malignancy originating from uveal melanocytes. Despite effective control of the primary tumour, metastatic uveal melanoma (MUM) occurs in approximately 20–30% of patients, primarily affecting the liver, with a poor prognosis and overall survival (OS). The unique molecular profile of UM, lacking *BRAF*, *NRAS,* and *KIT* mutations, limits targeted therapy efficacy. Chemotherapy and immune checkpoint inhibitors (ICIs) also show limited benefits, while tebentafusp has emerged as the first drug to improve OS, but this systemic treatment can be used only in HLA-A*02:01-positive patients. A French multidisciplinary panel developed evidence-based guidelines for MUM management presented in this review. Recommendations emphasise on comprehensive diagnosis, including liver biopsy and imaging, circulating tumour DNA (ctDNA) analysis, and high-definition HLA typing for HLA-A*02:01. Local therapies are proposed for patients with limited hepatic metastases, from liver surgery to isolated hepatic perfusion and chemo-embolisation for patients with more extensive hepatic involvement. Systemic therapy with tebentafusp is the standard of care for HLA-A*02:01-positive patients. For HLA-A*02:01-negative patients with extensive disease, treatment options are limited. They are encouraged to participate in a clinical trial, alternatively, percutaneous hepatic perfusion, ICI alone or in combination can be proposed. Treatment efficacy assessment includes response evaluation criteria in solid tumours (RECIST), tumour growth rate (TGR) analysis, and ctDNA dynamics. This consensus provides practical guidelines for French oncologists to optimise MUM management, integrating locoregional interventions, systemic therapies, and biomarkers to enhance patient outcomes.

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Introduction

Uveal melanoma, which originates from melanocytes within the uveal tract of the eye, is a rare malignant disease, and despite effective management of the primary tumour, approximately 20–30% of patients will eventually develop metastatic uveal melanoma (MUM) [1,2]. The liver is the most common site of metastasis, in up to 90% of patients. MUM has a poor prognosis, with a median overall survival of 12 to 16 months despite treatments[3–5]. Uveal melanoma has a distinct molecular profile from cutaneous melanoma, with no targetable mutations in *BRAF*, *NRAS*, or *KIT* genes [6], thus limiting the possible therapeutic options for targeted therapies. Conventional chemotherapy and immune checkpoint inhibitors (ICIs) have shown limited efficacy when metastatic [3,6–10]. Only recently, tebentafusp, a first-in-class immunotherapy consisting of a bispecific fusion protein that targets a peptide from the melanoma-associated antigen gp100 presented by the human leucocyte antigen (HLA) A*02:01, and the T-cell receptor CD3, activating lymphocyte antitumour response, has shown a benefit on the overall survival compared to chemotherapy or ICI monotherapy in HLA-A*02:01 positive patients (21.7 months [95% confidence interval (CI), 19.0 to 24.3] *versus* 16.0 months [95% CI, 12.9 to 19.5]) [4,11,12].

With the aim of providing guidelines for the management of patients with MUM, a multidisciplinary board of French experts gathered to establish a consensus based on a literature review, to help practitioners provide the best available care for these patients.

Methods

Fifteen pivotal questions on the diagnosis and therapeutic practices for MUM, along with propositions for treatment options, were listed by the first author (MR), an expert medical oncologist in this field. This document was shared with a panel of ten multidisciplinary French experts including specialists in medical oncology (SPN, EMN, MP, AD, TR), radiology (VS, FG), oncodermatology (CD) and liver surgery (PM). Then, these experts participated in a two-hour medical board organised in August 2024 with the support of Immunocore to share their opinions on MUM management with the help of these questions. With the authorisation of the experts, the panel discussion was recorded by the first author and shared with a scientific writer (FNP) for the writing foundation of this review article. The content of this article and drafts was not shared with Immunocore before acceptation by the journal.

Expert opinion

Initial work-up

Patients with suspected MUM must undergo (i) a biopsy of the tumour by percutaneous or surgical means to confirm the metastatic status and – if possible – for tumor biobanking, (ii) a comprehensive work-up to identify the full extent of metastases, and (iii) a pre-treatment assessment to guide their management. Several examinations can be performed to evaluate UM disease extension (*table I*).

Liver magnetic resonance imaging (MRI) with an extracellular gadolinium chelate injection and diffusion-weighted imaging is the most sensitive examination for the liver and is therefore mandatory for detecting focal lesions [13,14]. The use of hepatocyte uptake contrast agents (such as Gadolinium EOB-DTPA or Gadolinium BOPTA) is not recommended.

Assessment of extrahepatic metastases must include a thoraco-abdominopelvic computed tomography (CT) scan with an iodinated contrast agent injection for extrahepatic lesions or when

Table I
Disease assessment when metastatic

Organ	Examination
Liver	MRI with diffusion-weighted and T1-weighted/gadolinium sequences
	CT-scan with a contrast agent only if MRI is strictly contraindicated
Extrahepatic metastases	CT-scan with a contrast agent
	PET scan, especially if done with an iodinated contrast medium
Brain	Unnecessary, unless neurological symptoms are present May be considered after 2 years of metastatic disease
Blood	Complete blood count, renal and liver function tests, LDH
	HLA typing, specifically for HLA-A*02:01
	ctDNA if possible

ctDNA: circulating tumour DNA; CT scan: computed tomography scan; HLA: human leucocyte antigen; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging; PET: positron emission tomography scan; UM: Uveal Melanoma.

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MRI is strictly contraindicated [14]. As MUM cells do not always consume high levels of glucose, positron emission tomography (PET) scan is not sufficiently sensitive to replace liver MRI [15] but can be a valid option in patients presenting with mainly extrahepatic manifestations, especially if the PET scan includes an iodinated contrast medium As brain metastases are exceptional, brain imaging is not necessary unless neurological symptoms are present. However, it may be considered after two years of metastatic disease.

A comprehensive assessment of clinical laboratory parameters, including a complete blood count, renal and liver function tests, is required at initial work-up [14]. High lactate dehydrogenase (LDH) levels are indicative of a high tumour burden and are associated with poor prognosis [16]. Circulating tumour DNA (ctDNA) levels may also be determined at diagnosis to assist in monitoring disease progression, guiding therapeutic decision and assessing treatment response. Detectable ctDNA has shown to be associated with poor prognosis [17,18]. Importantly, as tebentafusp is indicated for HLA-A*02:01-positive patients, HLA typing must be performed early for all patients with suspected MUM and potentially for all patients with high-risk localised UM [19].

Local hepatic treatments

Most situations involve liver metastases. Local treatments can offer disease control and potential survival benefit for patients with limited liver metastases. Eligibility criteria for these treatments include (i) good general health condition of the patient with limited comorbidities, (ii) oligo-metastatic disease involving lesions accessible to margin-free resection (R0 resection), and (iii) completion of a full diagnosis work-up to verify the absence of inaccessible lesions.

Three main local approaches can be considered, either alone or in combination (*figure 1*):

- so far, surgery is the most effective local therapy to completely remove the metastases for selected patients. The median overall survival of patients after macroscopically complete resection was 35 months (95% CI: 23–55) while it was 21 months (95% CI: 4–42) in case of incomplete resection in a recent retrospective cohort of 86 patients who had surgical resection of liver metastases of uveal melanoma [20]. A comprehensive evaluation of the liver during intraoperative ultrasound might be required to detect additional intraparenchymal tumours and ensure completion of local treatment. The choice of surgical treatment may be guided by measuring

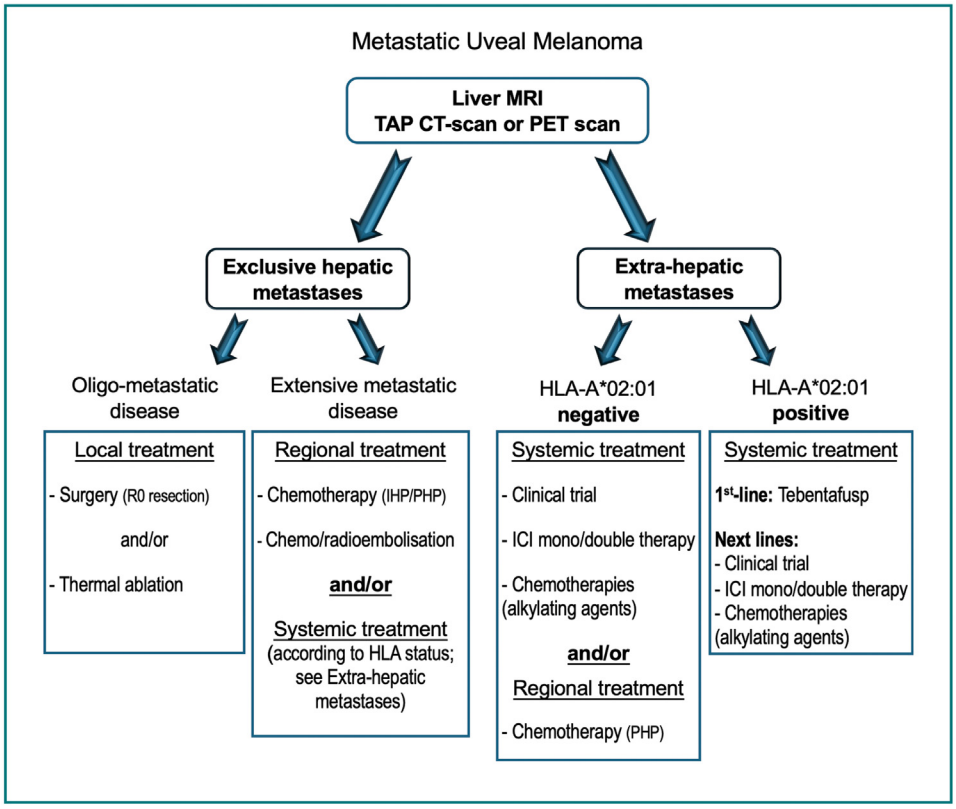

FIGURE 1

Decision flowchart for managing metastatic uveal melanoma

Abbreviations: HLA: human leucocyte antigen; ICI: immune checkpoint inhibitor; IHP: isolated hepatic perfusion; MRI: magnetic resonance imaging; PET: positron emission tomography; PHP: percutaneous hepatic perfusion; TAP CT-scan: thoraco-abdomino-pelvic computed tomography scan.

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ctDNA level before surgery as it can be of prognostic value for overall and relapse-free survival [17];
- radiofrequency, microwave ablation or cryoablation can be used alone or in combination with surgery to eliminate small intraparenchymal lesions or achieve R0 resection with a minimal impact on liver function [21]. Similar median disease-free survival and overall survival were found in patients treated with radiofrequency ablation plus surgery, and in those who underwent liver surgery alone (7 months *versus* 10 months for median disease free survival) and (28 months vs 27 months for median overall survival), respectively[22];
- stereotactic radiotherapy with MRI guidance and high-dose delivery to tumour sites may be used but should be restricted to cases where other local options are not feasible, due to limited evidence on this approach.

In cases of recurrent oligo-metastatic disease, local intervention can be repeated but should be limited to selected patients with long delay to second or beyond recurrences. According to the study of Servois et al. [23], exclusive and iterative local treatment combining liver surgery and radiofrequency ablation following an initial R0 surgical treatment is associated with long patient survival. However, these results, found in a small cohort of highly-selected patients, may not be generalisable. According to the opinion of the expert panel, if the patient presents a new late slow relapse, after a 12-month relapse-free period, a new local treatment may be considered, whereas, if the relapse occurs more rapidly, regional or systemic treatments should be considered instead of local hepatic treatments.

Regional hepatic treatments

Regional hepatic treatment can be suitable in cases with exclusive and limited hepatic metastases at any line of metastatic relapse. However, in the absence of comparative trial, tebentafusp is the standard treatment in metastatic recurrence not eligible to local treatments in HLA-A*02:01 patients (*figure 1*). In cases with extra-hepatic metastatic disease, systemic treatment should be privileged (see Section 0). A variety of regional options exist, each with their advantages and disadvantages regarding toxicity, cost, and availability [21–26].

Isolated hepatic perfusion (IHP) or percutaneous hepatic perfusion (PHP) with melphalan should be performed by ultra-specialised teams including perfusion pump specialists. Approximately 40% of patients with MUM can respond to one-time IHP with high-dose melphalan, as observed in the SCANDIUM phase III randomised controlled trial [25], but with significant toxicity [27].

For HLA-A*02:01-negative patients, PHP has been approved by the FDA and is included in NCCN guidelines as a locoregional treatment option, but its role as a first-line standard treatment remains unclear due to the lack of strong comparative data[28]. PHP may be considered in selected cases with liver-dominant disease and good performance status.

As shown in the EORTC 18021 phase III randomised trial [26], hepatic intra-arterial delivery of fotemustine can also significantly improve response rate and progression-free survival (PFS) compared to systemic (IV) fotemustine, although these benefits did not translate into an improved overall survival that was around 14 months in both arms. Chemoembolisation involves embolising the hepatic artery with chemotherapeutic agents similar to those used in hepatocellular carcinoma. While this therapy may provide short-term control, no definitive survival benefit has been established [21,24]. 90-Yttrium Selective Internal Radiation Therapy is generally not the preferred option due to suboptimal targeting, the challenge of delivering an efficacious dose to the tumour, and the potential for high hepatotoxicity.

Although none of the available regional treatments showed significant improvement in survival outcomes, they may help slow disease progression while new treatments are under development.

Systemic treatments

The choice of systemic therapy for MUM primarily relies on the HLA-A*02:01 status of the patient to determine eligibility for tebentafusp (*figure 1*).

Tebentafusp is currently the recommended first-line treatment in HLA-A*02:01-positive patients as it significantly extended overall survival compared to other conventional systemic treatment in first line [4]. Treatment with tebentafusp should be initiated as early as possible in less advanced disease as preliminary, but unconfirmed data suggest that low tumour burden is associated with better efficacy [11]. However, although MUM is usually resistant to ICIs, these treatments have shown an important anti-tumour effect in rare cases of patients with *MBD4* mutations, and may be considered in first-line regardless of their HLA status [9]. Patients with MUM should be screened for *MBD4* mutation as it may have therapeutic consequences, and for screening strategies for relatives carrying *MBD4* mutations.

There is no standard treatment for HLA-A*02:01-negative patients. Therefore, participation in clinical trials are encouraged. In the absence of any clinical trial, ICIs is the main option that can be proposed to these patients, either as monotherapy with the anti-PD1 antibody (nivolumab or pembrolizumab) or in combination with the anti-CTLA4 antibody (nivolumab + ipilimumab) according to two single-arm phase II trials [7,8] and the recent meta-analysis of Yamada et al. [10] including 41 cohorts for a total of 1414 patients with MUM. However, in the absence of any randomised controlled trial that compared mono and double ICIs, the combination of anti-PD1 + anti-CTLA4 has not proven its superiority over anti-PD1 monotherapy. Therefore, the preferred treatment option should be monotherapy, but the combination could be proposed to patients according to their age and comorbidities due to more frequent significant adverse effects associated with the combination. A single arm phase

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2 trial in 27 patients with MUM failed to demonstrate the superiority of nivolumab/relatlimab compared with historical cohorts treated with anti-PD1 alone [29].

The alternative may be alkylating chemotherapies, such as dacarbazine, temozolomide or fotemustine. However, all these treatments cannot be considered as standard as they are associated with low response rates and did not show improvement in overall survival [24]. For patients in advanced stages of the disease, supportive care must be offered for relieving symptoms and maintaining quality of life.

In the future, HLA-A*02:01-negative patients may benefit from the combination of protein kinase C inhibitor (IDE196) with MET inhibitor (crizotinib); recruitment is ongoing for a phase 3 trial as first-line treatment in HLA-A*02:01-negative patients following encouraging preliminary results in phase 2 [NCT03947385][30]

Tebentafusp protocol and related adverse events

Tebentafusp intravenous administration involves a specific protocol to minimise adverse events (AEs), particularly during the first infusions due to the risk of cytokine release syndrome (CRS) and acute skin-related reactions. Tebentafusp is initiated as inpatient therapy for at least the first three doses to allow close safety monitoring. The drug is administered using a 3-step dose escalation scheme: 20 µg on day 1, 30 µg on day 8, and 68 µg on day 15. Patients must be monitored overnight after treatment for the first 3 weeks, especially for pyrexia, hypoxia and hypotension which are the triad symptoms of CRS as defined according to ASTCT criteria [31]. Then, weekly administration can be done as an outpatient if no episode of CRS of grade 2 or higher has occurred. Treatment is continued until confirmed disease progression (see Section 0) or unacceptable toxicity. The safety issues related to tebentafusp are generally manageable using prespecified management algorithms.

If possible, antihypertensive medication should not be administered on the day of infusion for the first 3 infusions, to prevent hypotension. A basic cardiological examination, including an electrocardiogram, may be recommended before initiating treatment with tebentafusp because of the myocardial stress during CRS and vascular filling. Moreover, liver function tests should be monitored before the first tebentafusp infusion, to determine disease-related abnormalities and identify subsequent treatment-related AEs. Laboratory monitoring has to be repeated before each drug administration, weekly for the first three months, then every three weeks. For CRS prophylaxis, the expert group do not recommend systematic vascular filling before tebentafusp infusion, however corticosteroids may be considered in frail or elderly patients to prevent severe CRS. A basic dermatological assessment is also recommended before initiating tebentafusp for patients with preexisting conditions such as xerosis or atopic dermatitis to evaluate the risk of tebentafusp-induced cutaneous AEs and help manage them early.

The first three infusions of tebentafusp, which involve a gradual dosage increase, should be administered by an experienced team and should start early in the day to avoid the risk of CRS during the night shift. Monitoring of pyrexia, hypotension and hypoxia is very important as these symptoms can indicate CRS onset. Usually, CRS appears approximately 3 to 6 hours after infusion. A second venous access is required for early management of severe CRS. Blood pressure should be monitored every hour during the day, every 3 hours at night, and antipyretic therapy with paracetamol (acetaminophen) and antihistamines may be preventively administered 4 hours after tebentafusp infusion to limit the symptoms. In the event of CRS, close monitoring is required and the episode should be managed according to its severity grade (including saline infusion, corticosteroids and tocilizumab in resistant CRS). Exceptionally, patients may present an extended grade 1–2 fever on the following days even after several months of treatment. In these rare cases, punctual intakes of non-steroidal anti-inflammatory drugs may be considered.

Cutaneous reactions are the most common AEs of tebentafusp treatment reported in up to 70% (pruritus) or 80% (rash) of patients [11]. Mild skin toxicity of grade 1, according to the common terminology criteria for AEs (CTCAE v5) [32], can be managed using non-pharmacological measures such as cold showers and topical interventions. For CTCAE grade 1 or grade 2 pruritic rash, emollients and non-sedating anti-histamines (cetirizine, levocetirizine, desloratadine) may be administered, but in cases of pruritus affecting sleep, prescription of sedating anti-histamines (polaramine) may be required. For persistent CTCAE grade 2 or grade 3 pruritus, treatment with potent to very potent topical corticosteroids (betamethasone 0.05% or clobetasol propionate 0.05%) may be added on top of emollients and anti-histamines. In most cases, symptoms partially resolve in few days without the need for corticosteroids and completely resolve in few months, with no long-term sequelae. If symptoms do not resolve with these treatments, patients should be referred to an expert dermatologist.

Treatment interruptions may occasionally be necessary due to patient needs or scheduling challenges. However, interruptions should be avoided whenever possible during the initial 4-week dose escalation period as this phase is crucial to establish the therapeutic escalation and monitor patient tolerance. Missing doses during this period may increase the duration of AEs. Once patients reach the weekly maintenance phase at 68 µg, limited breaks of one to three sessions are permissible for practical or medical reasons, knowing that there can be mild skin reactions on resumption of treatment. Patients requiring longer treatment interruptions should undergo careful assessment, as the potential for adverse skin reactions, and potentially CRS, increases with longer intervals between doses. In all cases, the decision to pause or resume treatment should be guided by clinical judgment, patient stability, and AE history. The potential

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consequences of these interruptions on tebentafusp efficacy are not fully known. However, data from the IMCgp100-202 trial suggest that occasional (i.e. one or two) missed doses do not significantly impact overall survival, although prolonged interruptions should be avoided when possible[33]

Tebentafusp efficacy evaluation

Treatment efficacy should be assessed regularly using the same work-up as for the initial assessment of MUM (*figure 2*). The first evaluation is recommended 12 weeks after tebentafusp start. Standardised criteria such as RECIST 1.1 (Response evaluation criteria in solid tumours at https://recist.eortc.org/) are commonly used to assess changes in tumour size and distribution. If the patient presents with treatment response, stable disease or limited progressive disease according to RECIST 1.1, reassessment should be carried out with a 12-week interval during treatment course. But, if the tumour is quickly progressing, the assessment should be repeated earlier, at 6 weeks before returning to a 12-week interval.

Tumour growth rate (TGR) can also provide a valuable quantitative evaluation of MUM progression [34,35]. The TGR is expressed as the percentage change in tumour volume per month and is calculated as follows: %TGR = 100 × [exp (TG)–1], where TG = 3 × log (D2/D1)/time (months) with D1 and D2 representing the sum of the largest diameter of target liver lesions seen on two examinations. Ideally, imaging procedures conducted prior to treatment can provide the pre-treatment growth rate (TGR0), and then a decrease in TGR values during tebentafusp therapy indicates a potential therapeutic effect. Changes in the curve of TGR can be followed over the treatment course even in the absence of TGR0. The use of TGR assessment should be encouraged as it can be more accurate than RECIST (or iRECIST), especially for identifying slowing of tumour progression which is often observed at the beginning of the treatment.

Emerging evidence also supports the value of ctDNA as a biomarker for monitoring MUM progression and treatment response. Indeed, some studies showed that detection of ctDNA at the start of tebentafusp treatment was associated with poorer prognosis, whereas a decrease in ctDNA levels of at least 90%–100% within 9 to 12 weeks of tebentafusp therapy, regardless of best RECIST response, was predictive of longer overall survival [4,17,18,36,37]. Several techniques may be used to measure ctDNA, including next-generation sequencing (NGS) panels or droplet digital PCR (ddPCR). Platforms using ctDNA measures should be encouraged to cross-validate their results with a reference technique. The integration of ctDNA monitoring into clinical practice could enhance treatment decision-making, especially in patients with ambiguous imaging results. However, ctDNA does not substitute to radiological assessment, and further research is required to evaluate their respective roles.

Given the limited treatment options available for patients, tebentafusp may be continued for a further 6 to 12-week cycle in case of secondary tumour progression (i.e., several months after initial response or stabilisation), especially when disease progression is limited and non-threatening, or when the tumour has not yet returned to its initial volume. A benefit on the overall survival has indeed been found with tebentafusp treatment even in patients who progressed at the first evaluation [4,11]. There is currently no evidence regarding de-escalation of treatment. The decision to interrupt tebentafusp after one to two years if stable disease and negative ctDNA, might be considered in expert centers.

Second-line treatments after tebentafusp

When patients experience secondary resistance to tebentafusp following an initial period of response, treatment options are limited. Patients should therefore be encouraged to participate

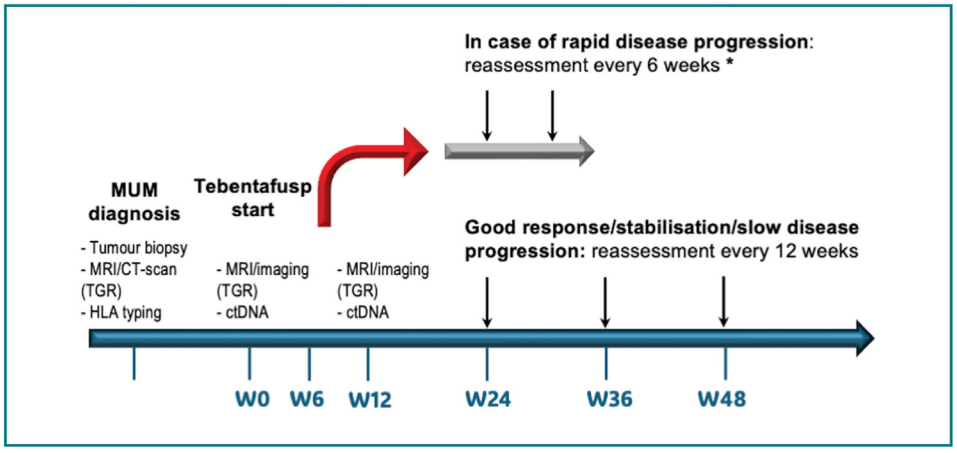

FIGURE 2

Timelines for the evaluation of tebentafusp treatment efficacy.

*Assessment of the disease progression can return to a 12-week frequency if the tumour is stabilising. Abbreviations: ctDNA: circulating tumour DNA; CT-scan: computed tomography scan; HLA: human leucocyte antigen; MRI: magnetic resonance imaging; TGR: Tumor Growth Rate; W, week.

in clinical trials. In the absence of trial, the second-line options are the same as first-line options in HLA-A*02:01-negative patients (*figure 1*). Anti-PD1 monotherapy should be prioritised because of their potential for synergy with tebentafusp [38]. It is important to note that ICI treatment can be started as soon as the day following the cessation of tebentafusp because of its very short half-life and the similar safety profile of the ICI/tebentafusp combination found in early phase trials [24,39].

Conclusion

This expert opinion, based on clinical evidence, provides practical recommendations for the diagnosis and management of MUM, which is a rare but challenging cancer with poor prognosis. Treatment decisions should benefit from a tailored, multidisciplinary approach involving experts in MUM with experience in both local/regional and systemic treatments. Systemic treatment with tebentafusp was shown to significantly improve overall survival in HLA-A*02:01-positive patients and must be considered as the standard first-line treatment in patients not suitable for liver surgery. However, for HLA-A*02:01-negative patients or those who develop secondary resistance to tebentafusp, treatment options are still limited. The use of novel and non-invasive tools, such as ctDNA and TGR, to monitor disease progression and treatment response should be extended in clinical practice to allow physicians rapidly adapt the therapy. Future research should also focus on novel agents, combination strategies, and the potential of immune modulation to expand the therapeutic landscape for MUM management.

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