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Uncertainty and hope in people with metastatic uveal melanoma in the era of immunotherapy and targeted treatments: a theory-based qualitative study

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Abstract

Background The advent of immunotherapies and targeted treatments has improved survival for some people with metastatic cancer but also increased prognostic uncertainty. To inform clinician-patient communication and supportive care, this study explored uncertainty-related coping among people with metastatic uveal melanoma (mUM) – a disease for which treatments have emerged especially suddenly.

Methods A qualitative approach was taken using semi-structured interviews. Participants with mUM were recruited through consumer organisations internationally. Interviews explored participant perspectives on the impacts of uncertainty and their related coping strategies. Analysis involved inductive coding followed by deductive coding against Mishel's (1988) theoretical framework of uncertainty in illness.

Results Seventeen people participated, including 10 from Australia. Participants described experiencing uncertainty as disempowering but also leveraged the opportunity it presented for remaining hopeful. Some participants used meta-cognition– alluded to as 'tricking' or 'fooling' themselves - to manage inconsistency between hoping for an exceptional response and accepting that benefits were likely to be modest at best. Most participants were able to maintain everyday normalcy but struggled to discuss their illness and treatment with family and friends. Participants reported heightened anxiety in the lead-up to routine scans and while awaiting results.

Conclusions Coping with uncertainty in the era of immunotherapy and targeted treatments involves 'hoping for the best while preparing for the worst'. Supportive care is especially needed at the time of scans. Some patients may also benefit from help with talking to their social networks. Head-to-head comparisons are needed of differing psychological interventions.

Keywords Advanced cancer, Immunotherapy, Targeted treatments, Uncertainty, Coping, Qualitative

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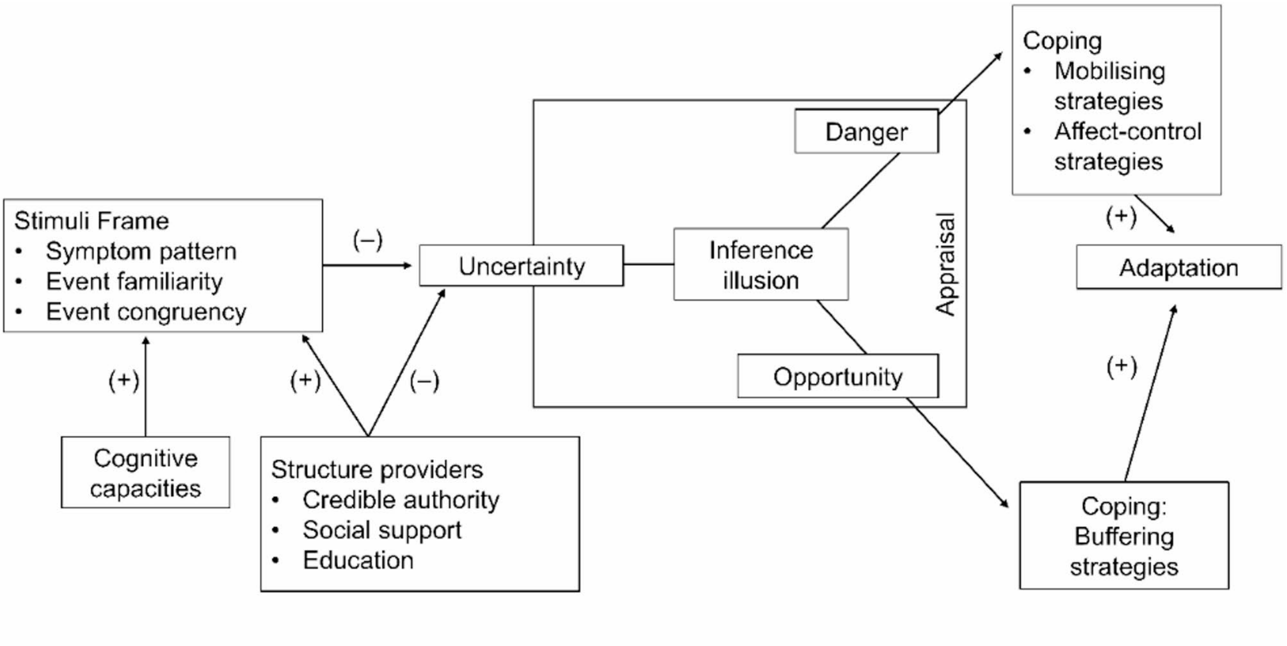
Background

In the theoretical literature, patients' emotional responses to ill health have been conceptualised variously according to health condition [1]. In the cancer field, there has been special focus on fear of disease recurrence and progression following treatment [2, 3]. Substantial research has also focused on how patients with advanced cancer cope with existential challenges as they near the end of life [4]. However, fewer studies have focused on the emotional responses of people with advanced cancer in the context of immunotherapy and/or targeted therapy. These treatments have resulted in an exceptional response for a small proportion of patients but offered more modest benefits to survival for the majority [5]. Uncertainties about treatment access and efficacy have been identified as serious concerns for patients in this population [6–8]. Indeed, in a recent meta-synthesis of qualitative research, Langmuir et al. (2023) identified uncertainty about treatment efficacy to have major impacts on emotional, social and financial wellbeing [9]. Consistent with a theoretical framework by Mishel (1988, 1990) [10, 11] (Fig. 1), Langmuir et al. found that patients vary in their appraisal of uncertainty as 'dangerous' or an 'opportunity', depending on the information and social support they receive and the trust they place in their medical teams. The synthesis found that patients who cope better may be those who are able to accept they lack control over treatment efficacy and instead focus their efforts on managing their emotional response by reframing uncertainty as affording positive potential and 'living in the present' rather than worrying about the future. Mishel's framework posits various characteristics of the 'stimuli frame' and 'structure providers' that might contribute positively or negatively to patients' perception of uncertainty, which were less explored by Langmuir and colleagues.

A UK consensus workshop held in 2023 identified clinician-patient communication and support for coping to be the highest priorities for future research on uncertainty related to serious illness [12]. This may be achieved through best-practice clinician-patient communication strategies highlighted in a review by Simpkin and Armstrong (2019), which emphasised the need to: ask patients about their preferences for the amount, type and format of information; ensure ambiguity is explicit (for example, giving range estimates for outcomes rather than averages); provide reassurance that support will be ongoing even if outcomes are poor; and clarify contingency plans [13]. However, immunotherapy may pose special challenges for clinicians wanting to balance realistic prognostic information with communication aimed at maintaining patient hope [14].

Metastatic uveal melanoma (mUM) presents a paradigmatic context for studying the experience of uncertainty and related communication in the era of modern therapies. Uveal melanoma is a rare tumour that has a 40–50% chance of metastasising after early-stage treatment [15]. Until recently, mUM had no approved treatments. However, in 2021, a trial was published that found a first-in-class immune-mobilizing monoclonal T cell receptor called tebentafusp improved survival compared



Note: Adapted from: "Uncertainty in Illness" by M. H. Mishel, 1988, Journal of Nursing Scholarship, 20(4), Figure 1, p226, with permission of John Wiley and Sons

Fig. 1 Mishel's (1988) theoretical framework of perceived uncertainty in illness [10] to investigator choice of treatment in patients with HLA-A*02:01-positive muM. Overall survival was 73% versus 59% at 1 year, and 27% versus 18% at 3 years, with a median survival of 21.6 months (95% CI, 19.0 to 24.3) versus 16.9 months (95% CI, 12.9 to 19.5) [16, 17]. Even at 4 years, the overall survival rate is 14% [18]. Additionally, Tebentafusp is unusual in that even patients whose tumour shows no objective response still derive some survival benefit, further adding to uncertainty. More recently, several promising agents (e.g., darovasertib and crizotinib) are being tested in registrational trials and may continue to produce improvements in survival over the coming years [19]. However, like tebentafusp, these are likely to have limited eligibility criteria and availability through universal healthcare systems, and variable efficacy between individuals. The only previous qualitative study exploring coping in people with mUM was conducted before treatment options emerged [20], and further research is needed to explore how patients' emotional response has been impacted by the new treatment landscape.

To inform clinician-patient communication and supportive care, this study explored uncertainty-related coping among patients with mUM, using Mishel's framework to build on findings from similar studies focusing on other cancer types as synthesised by Langmuir and colleagues. mUM serves as a prototypical example among advanced cancers for which new treatments are starting to emerge and thus offers a case study for developing uncertainty-related supportive care.

Materials and methods

A qualitative approach was taken to enable in-depth exploration of patient experience of uncertainty and related coping [21]. The study was conducted between August 2022 and October 2023, and received ethical approval from St Vincent's Hospital Sydney Human Research Ethics Committee (2022/ETH01013). All participants gave informed verbal consent. Reporting adheres to the COnsolidated criteria for REporting Qualitative research (COREQ) [22]. As has been reported previously [23], the study was designed to explore impacts of mUM and its treatment on quality of life more generally, as well as perspectives on the content validity for mUM of quality of life questionnaires designed for early-stage UM or other cancer types. Aside from uncertainty, participant concerns focused largely on time, travel and financial burdens from new generation treatments, which were available only at specialist cancer centres and rarely subsidised by government schemes. Side-effects were reported to include fatigue, skin reactions and fever, but these were described as short-term and tolerable.

Participants

Eligible participants were adults (aged ≥ 18 years) living with mUM. Patients were excluded if they were unable to provide informed consent and/or participate due to cognitive impairment or limited proficiency in English.

Due to the relative rarity of uveal melanoma, sampling was international to enable an adequate sample size. Patients were recruited through email lists for consumer organisations including Cure OM (USA), Melanoma Patients Australia and Rare Cancers Australia, OcuMelUK, Ocular Melanoma Ireland and Ocumel Canada, as well as social media. Australian recruitment also occurred through outpatient services at two quaternary referral centres in Sydney and Melbourne. The approach to recruitment meant that the number of people who were invited but did not participate could not be recorded.

Data collection

Data were collected by means of semi-structured interviews conducted via video-conference (Zoom or Microsoft Teams) to enable international participation, minimise burden and reduce risk of COVID-19 transmission. Interviews were conducted by one (TL) or two (TL, CN) researchers– a male social scientist (PhD) with experience in qualitative research on experiences of individuals facing life-limiting illnesses, and a female health economist (PhD) with no experience of qualitative research but expertise in questionnaires. The interviewers had no prior or continuing relationships with any of the participants. Participants knew the researchers were not involved in their care and the purpose of the research. To our knowledge, no one else was present besides the participants and researchers.

The interview topic guide was developed for this study (Supplementary file 1). Interviews began with open-ended questions about the impacts of mUM and its treatment on quality of life. As noted above, one line of questioning focused on the content validity of relevant questionnaires. A second line of in-depth questioning focused on the impact of uncertainty after it emerged as the most important impact for most participants, warranting deeper exploration. Uncertainty-related questions focused on its impact on the person's psychological wellbeing and relationships with family and friends, ways of coping with it, and related communication and support from their medical team.

In addition to qualitative data, patients were asked to provide demographic information (gender, age), time since initial diagnosis and metastases, and treatments received.

Interviews were audio-recorded and transcribed, after which data were deidentified. Recruitment continued until 'information power' was reached for quality of life issues [24]. No repeat interviews were carried out. Data were imported into NVivo v12 software for management and analysis.

Analysis

Analysis of data on uncertainty used an integrated approach involving both inductive and deductive coding [25]. Initially, transcripts were coded inductively line-by-line to ensure that insights shared by participants were captured regardless of their fit to established theory. The next step of analysis was more deductive and involved classifying codes according to the domains of Mishel's (1988, 1990) framework of perceived uncertainty in illness [10, 11], identifying any that did not easily fit.

TL and CN coded the initial five patient interviews line-by-line, with coding discrepancies resolved by discussion until consensus was reached. CN conducted inductive coding for the remaining interviews. Coding occurred at intervals after three consecutive interviews, so that emerging issues could be revisited during the next round of data collection for verification and further development. Deductive coding against Mishel's framework was conducted by TL. Due to the time required to complete the analysis within the context of mUM's limited prognosis, the verification of results by participants was infeasible.

Results

Sample characteristics

Seventeen patients took part in the study. All participants had access to immunotherapy and/or targeted therapy. Fourteen participants were undergoing treatment at the time of being interviewed, two were deliberating treatment options, and one had stopped with no anticipation of further treatment. The mean duration of interviews was 60 min. Table 1 summarises participant characteristics. Two participants from New Zealand were living in Australia to access tebentafusp, while another received darovasertib/crizotinib therapy in Australia before returning to New Zealand.

Qualitative analysis

As anticipated, uncertainty and hope featured prominently in participants' accounts of their emotional response to mUM and its treatment. Unless they had recently commenced a new treatment, participants reported feeling well enough to return to normal activities of daily living. Uncertainty intruded on normalcy as a worrying presence "*at the back of my mind*" (P01, Australian woman aged 31–40) ("*I can tell you that 99% of the patients with metastatic disease have this on their mind all the time*" (P05, European woman aged 41–50)) and a difficulty with planning work, social commitments and recreational activities beyond the immediate future ("*[when faced with a planning decision] I go, 'well, am I here [still alive] next year or am I not here next year?' I don't know*" (P03, Australian woman aged 41–50)).

Coding against Mishel's theory of perceived uncertainty in illness identified content relevant to all components of the framework except for 'cognitive capacity'; no-one commented on impacts to cognitive processing from disease, treatment or any other cause. Coding in relation to other components of Mishel's framework is summarised as follows. All data on uncertainty could be assigned easily to a component of the framework.

A. Stimuli frame

Symptoms Mishel suggests that illness-related uncertainty is influenced by consistency in the frequency and severity of symptoms and the degree to which this enables patients to identify patterns affording explanation. Participants reported having grown accustomed to visual impairments from treatment for early-stage uveal melanoma and most reported few, if any, further symptoms from mUM. Although participants welcomed being asymptomatic, several reported being emotionally challenged by the illusory sense of normalcy ("*without the lump under my arm, I could probably convince myself I was healthy on every day except Thursday when you're sat on the ward*" (P02, British man aged 51–60); "*I always joke when people ask me how I feel - my answer usually is 'I feel like they're telling me I have something that I don't have'*" (P10, Canadian man aged 71–80); "*I felt as if I was living a lie; I'm really well, I went to the gym [and yet I'm seriously ill]*" (P15, Australian woman aged 61–70)). In contrast, two participants with ongoing side-effects spoke about these being constant reminders ("*I think I'm reminded all the time by my lack of energy*" (P14, New Zealand woman aged 61–70 receiving treatment in Australia); "*being nauseous and stuff, that just keeps throwing it right in my face. So it's hard not to think about it*" (P04, New Zealand woman aged 61–70)), and one person with signs of mUM monitored these in a way that approached hypervigilance ("*I've got a constant reminder… I have one tumour that's palpable in my lymph node… every time you have a shower, you sort of know whether it's increased in size, decreased or remained static. So I guess there's a psychological impact from that. What it is exactly, I don't know*" (P02, British man aged 51–60)).

Event familiarity Mishel suggests that uncertainty is exacerbated by novelty and complexity in the healthcare environment that prevent the patient from developing a 'cognitive map' to aid predication of events. Several participants highlighted the rarity of mUM and newness of treatments as key sources of uncertainty ("Y*ou have to [trust your medical team]. You can't doubt them because*

Table 1 Characteristics of 17 participants with metastatic uveal melanoma

Characteristic	Number (%)
Female gender	10 (59%)
Country of treatment	
Australia	10 (59%)
United Kingdom	2 (12%)
New Zealand	1 (6%)
Switzerland	1 (6%)
Sweden	1 (6%)
USA	1 (6%)
Canada	1 (6%)
Age (years)	
31–40	2 (12%)
41–50	3 (18%)
51–60	4 (24%)
61–70	6 (35%)
71–80	1 (6%)
81 or over	1 (6%)
Time since diagnosis of primary uveal melanoma	
< 3 years	2 (12%)
3–4 years	1 (6%)
5–10 years	7 (41%)
> 10 years	7 (41%)
Treatment for primary uveal melanoma	
Enucleation only	4 (24%)
Plaque brachytherapy only	7 (41%)
Plaque brachytherapy followed by enucleation	3 (18%)
Laser therapy followed by enucleation	1 (6%)
Proton beam therapy only	1 (6%)
Unclear	1 (6%)
Time since diagnosis of metastases	
< 1 year	5 (29%)
1–2 years	4 (24%)
> 2 years	8 (47%)
Site of metastases	
Liver	16 (94%)
Bones	2 (12%)
Lung	2 (12%)
Pancreas	1 (6%)
Kidney	1 (6%)
Breast	1 (6%)
Treatment for metastases	
Systemic therapy Tebentafusp Ipilimumab and nivolumab Darovasertib and crizotinib Pembrolizumab Darovasertib alone Nivolumab and relatlimab	17 (100%) 10 (59%) 4 (24%) 3 (18%) 2 (12%) 1 (6%) 1 (6%)
Surgery	6 (35%)
Radiotherapy	3 (18%)
Chemotherapy	2 (12%)

this thing's so rare as well. No choice there have you really?" (P17, Australian man aged 51–60)). All participants were familiar with oncology centres from their early-stage treatments. However, tebentafusp posed new challenges, requiring hospitalisation at commencement and long-distance travel for weekly infusions over an indeterminant period with no breaks ("*friends or family who are more familiar, I guess, with the chemotherapy world, would be, like, 'how many rounds to go? How many months to go?' I don't have an end date*" (P01, Australian woman aged 31–40)). After some weeks, participants became familiar with the treatment routine and accommodated this within their everyday lives. This contrasted sharply with scans assessing the efficacy of treatment, which continued to elicit "*scanxiety*" (P07, Australian man aged 31–40; P11, American man aged 71–80; P15, Australian woman aged 61–70) despite occurring at regular intervals during treatment. Indeed, participants described the days leading up to scans and awaiting results to be the most challenging periods they faced ("*those routine scans, and I'm sure it's the same for every cancer, they're brutal with the anxiety and the pain you put yourself through about if it spreads, if it spreads if it spreads*" (P01, Australian woman aged 31–40)).

Most participants were accessing treatment as part of a clinical trial, on compassionate grounds or through insurance, with several commenting on the novel and complex processes they had to learn to navigate, and the lack of certainty that access would continue as long as they needed the treatment ("*I'm still in the extended access program in [country]... so [pharmaceutical company] is still giving the drug for free. This is causing a problem for me now, because insurance is not covering it [in the country where my husband is]. I mean, we are working on it. I don't know what the outcome is going to be*" (P05, European woman aged 41–50)). Participants expressed worry about their ability to self-fund treatment and the potential they might have to decide whether to pursue expensive new treatments if their current one failed, especially the financial burden this might place on their family for increasingly uncertain gains with each new line of therapy ("*if you have to take ongoing medication that's expensive, then that's a possibility, that that could be a financial burden on either me or my family*" (P09, Australian woman aged 51–60)).

Several participants expressed worry about the screening process for new treatments and anxiety while waiting to hear if they were eligible. Participants expressed disappointment and/or frustration when they were found to be ineligible ("*I've read a lot about the drug [tebentafusp] and how it works, and I've been waiting for it to be approved. It was disappointing when I couldn't [receive it]– that it's not for me*" (P06, Swedish woman aged 61–70)).

Around half of the participants saw clinical trials as an important way to expand their treatment options (*"[If] I was in a position right now where I had no treatment available to me, I would be jumping all over the chance of going on a trial."* (P10, Canadian man aged 61–70)). While altruism was a motivational factor for at least one participant ("*I'm well aware that trials aren't really for my benefit, they're for other people's benefit, and therefore [eligibility] doesn't bother me*" (P11, American man, aged 71–80)), the majority emphasised access to new treatments as being their primary driver. Two participants preferred trials that did not involve randomisation so that they could reduce uncertainty as to whether they would receive the investigational agent ("*phase two also includes the use of placebo. Both [of my oncologists] agreed that really wasn't the best option for me; they wanted me to have the full drug*" (P15, Australian woman aged 61–70); "*my idea of a trial, especially a [randomised] phase two trial, is that it is not for me - it is for people who come later. It's like what we're doing here is not going to benefit me whatsoever... I don't know if I want to put my family through false expectations... if they say, 'well, phase two, we're going to have a placebo arm', I'm not sure I'm happy*" (P11, American man aged 71–80)). Another participant expressed reservations regarding the safety aspects of novel treatments in early-phase trials, preferring to wait until these had been further tested ("*I'd rather explore trying to get access to a drug with less side effects, for which there's some evidence it might do something, first*" (P02, British man aged 51–60)).

Event congruence Event congruence is the degree to which events conform to what was expected. Treatment side-effects conformed to expected patterns in timing and duration especially for tebentafusp ("*I was prepped [that I'd get a rash on the first infusions]. It is rough but it does ease off*" (P01, Australian woman aged 31–40)). Whilst side-effects were regarded as unpleasant, their predictability was reassuring to participants, some of whom viewed them as signs that the treatment was working against their cancer ("*the skin rash, the first few treatments was unbelievable. I don't think I could go through that again. It was incredible. But I always say that's probably why that it's working so well... [The oncologists] have a saying, "no rash, no good."* (P10, Canadian man aged 61–70)).

B. Structure providers

Structure providers is the term used by Mishel to refer to factors that influence people's ability to understand and interpret their disease and treatments in ways that might ameliorate uncertainty.

Education and credible authority Most participants valued upfront and reliable information about mUM and its treatment from their healthcare teams, including acknowledgement by clinicians when they themselves were uncertain ("*they're about as lost as I am sometimes. And that's not casting aspersions*" (P11, American man aged 71–80); "*one of the doctors said to me, 'we don't really know what your prognosis [is] because we are still finding out about this drug*'" (P16, New Zealand woman aged 51–60 receiving treatment in Australia)).

Some participants sought additional information online to feel more "*in control of what's going on*" (P09, Australian woman aged 51–60), while others were more "*guarded*" (P10, Canadian man aged 61–70) about the value of online searches, preferring to rely on their doctors for sourcing, curating and interpreting information for them ("*just trust your doctors and stay off the internet*" (P01, Australian woman aged 31–40)). Variability in this regard was related to further preferences concerning the degree to which patients wanted to be involved in treatment-related decision-making, ranging from those who preferred to be the decision-maker ("*I read a lot and I try to be on top of the research, to be my own advocate, because else I wouldn't be where I am now... you have to be very proactive... other people, if they stick to one doctor, to one place, they must be very lucky if they survive a long time... so it becomes your job to stay alive*" (P05, European woman aged 41–50)), through those wanting a shared decision-making approach ("*it is nice to have someone give me ideas about which option might be better*" (P09, Australian woman aged 51–60)), to those who preferred their medical team make the decisions on their behalf ("*I've definitely taken on board the medical side of things from [the doctors], and really haven't asked too many questions*" (P15, Australian woman aged 61–70)). Participants who were least information-seeking and preferred decisions to be made by their medical team were more likely to praise the care they had received, emphasising the importance of trust and support ("*I don't get too overwhelmed with it because having that trust and knowing they [my medical team] want to keep me alive as much as I want to be alive*" (P01, Australian woman aged 31–40)). Conversely, participants who sought information from sources other than their medical team and wanted a high level of control over decisions were more likely to perceive a breach of trust in the form of a delay in diagnosis or poor treatment choices on the part of medical teams ("*[I've encountered] some relative incompetence in treatment and arranging things.... [So] I just went and pulled out of the clinical trial, emailed the lead author and said, 'this is my situation, do you know anywhere in the UK that takes this area of patients?*'" (P02, British man aged 51–60)). For one of these participants, mistrust extended beyond individual clinicians to a perceived lack of collaboration between oncology centres ("*it is horrible as a patient to see how little the centres work together in such a rare disease with so few patients.... If all the knowledge [was] open to everybody, the situation would look different, I think*" (P05, European woman aged 41–50)). Notably, this participant drew on peer support networks ("*there is a constant exchange of treatments and of trials, like people write which trial they're on, what side effects they have, what response they have and what their doctors say*" (P05, European woman aged 41–50)) and trusted family members and friends for professional expertise to supplement advice from their healthcare team ("*in my family, I have a professor in [relevant fields]... and my daughter... has access to all the other [journal article] papers. So if I need something or if I need to know, is this really peer reviewed and if it really is trustworthy... I send it to her and she checks it because I'm not a scientist*" (P05, European woman aged 41–50)).

For some participants, taking a leading role in decision-making appeared to confer a sense of control that compensated for loss of agency in relation to the disease; however, the lack of "*a defined treatment path*" (P09, Australian woman aged 51–60) for mUM also conferred a burden of decisional conflict ("*I just like to know that when I make these decisions, they're the right decisions and there's no regret*" (P01, Australian woman aged 31–40)).

Social support While many people drew emotional support from close family and friends, their apparent good health meant that more extended networks sometimes struggled to understand their prognostic uncertainty ("*when they see me, you see, because I look so well, then I found that probably people sort of don't understand*" (P14, New Zealand woman aged 61–70 receiving treatment in Australia); "*my extended family over in the UK, they tend to forget about it because I don't look unwell*" (P15, Australian woman aged 61–70)).

Several participants voiced concern about family members dealing with current uncertainty or coping emotionally and/or practically after they had died ("*I think what might happen in the future [for my family] is the most painful thing... the eventuality that I might die*" (P07, Australian man aged 31–40); "*I wish my wife didn't have to deal with this*" (P10, Canadian man aged 71–80)).

Participants derived emotional support from the shared understanding they experienced when talking with fellow muM patients but also risked emotional burden when others succumbed to their disease, experienced by some as "*survivor's guilt*" ("*I think it can't seem very fair to you [the mother of a patient who died from mUM] that I'm 20 odd years older than your daughter and I'm still knocking about*" (P12, British man aged 41–50)).

C. Appraisal

Appraisal refers to a person's ability to classify uncertainty within existing frames of reference or modify these frames to accommodate. Appraisal relies on two major processes: 'inference' regarding similarities between the current situation and those previously experienced, and 'illusion' by which people selectively interpret uncertainty in ways that align it with a positive worldview.

Inference Some participants distinguished between uncertainty *outside* versus *within* their control, with the latter causing more concern because it conferred a responsibility and risk of making mistakes ("*whether the treatment works or not, that's sort of fixed, and also whether the disease spreads or not is also dependent on whether the treatment works or not. So, those sorts of things I can control a little bit, because I can decide what sort of treatment to have, but it's the uncertainty of what to do next that, I think, is the most difficult for me*" (P09, Australian woman aged 51–60)).

Several participants discussed the temptation of inferring their prognosis from other patients who they met at the hospital or through peer support networks, concluding that this was inadvisable either because of inexplicable variability ("*I would rather kind of just explore my own path and not assume that because other people have this kind of prognosis that that's going to be me*" (P16, New Zealand woman aged 51–60 receiving treatment in Australia)) or because of the challenge it posed to remaining emotionally positive ("*it's somehow easier to tell yourself you're going to be a person that does well on it [tebentafusp] if you're not surrounded by people that are not doing well*" (P12, British man aged 41–50)).

Illusion While all participants had been emotionally distressed by news of the cancer metastasising, they varied in the degree to which they reported this to be a "*shock*" (P09, Australian female aged 51–60; P10, Canadian man aged 61–70). Some participants explained feeling this way because they were asymptomatic ("*when it was picked up again, [I] felt totally fine– absolutely shocked. It's just weird to know this is happening on the inside but I feel so good.*" (P01, Australian woman aged 31–40)), but a few were "surprised that it took so long" (P13, Australian man aged ≥ 81) to metastasise. Although some had limited warning from their medical teams about the high risk of recurrence, others were shocked despite having been well informed ("*even though I knew it was a big possibility, it really hit me like a tonne of bricks when it actually came up. So, emotionally, that was really hard*" (P15, Australian female aged 61–70)).

Nearly all participants leveraged the 'opportunity' presented by uncertainty to give themselves and their families hope. Indeed, participants often exaggerated the level of uncertainty regarding prognosis to increase the possibility that they might be an exceptional responder ("*I think nobody really knows. I accidentally saw something on Google that you've normally got 12 months, so I've got five, six months. But then this new medication's only been around for a short period of time, so I'm hoping [the prognosis is wrong]*" (P04, New Zealand woman aged 61–70)). However, individuals varied in the degree to which they maintained awareness that they were using this as a protective coping strategy. Participants who appeared to be coping well were able to exploit the emotional opportunity posed by uncertainty whilst simultaneously retaining insight at a cognitive level that the odds were against them being an outlier for survival ("*I hope I'm not fooling myself. I do worry about that a little bit. Maybe why didn't I freak out when he told me I had one of the worst diseases you can get? But it's, like, 'Okay, there it is'* (P11, American man aged 71–80)). One participant extended the opportunity he derived from uncertainty to include physical as well as emotional health ("*if you trick your body into thinking you're healthy, you stand a better chance... [this] could well be just a load of shit... [but] it's served me well to this point, so we'll go with it*" (P12, British man aged 41–50)). Several participants also reported trying to "*ignore*" (P10, Canadian man aged 71–80) their illness between treatments to better enjoy times free from side-effects.

D. Coping

According to Mishel, people's ability to cope with uncertainty depends on the degree to which they can reduce it and/or manage their emotional response.

Mobilising strategies to reduce uncertainty As noted above, a small number of participants self-monitored for signs and symptoms and sought information from the internet, peers and family to supplement advice from their medical teams. Another mobilising strategy not mentioned by Mishel was to make diet and exercise changes with the aim of increasing fitness for treatment or, in one case, to work directly against the cancer ("*then I thought 'OK, maybe I should support the healing a bit. Not just lay in my bed– get up*" (P05, European woman aged 41–50)). The one participant who had chosen to stop treatments switched his attention to maintaining health and wellbeing for as long as possible ("*I've had open discussions with both my oncologists knowing that my life, my end is six months, 12 months, two years, or who knows... I'm in fairly good physical condition, and I'm an active person*" (P08, Australian man aged 61–70)). None of the participants currently on treatment had considered stopping or turning down new opportunities as a way of reducing uncertainty or because side effects outweighed benefits to survival. However, a small number could foresee a scenario where this might be in their best interests ("*this idea of extending life, but also trying to do it in a way that maintains my quality of life, is kind of important to me*" (P09, Australian woman aged 51–60); "*it seems that prolonging is the best, but when you're alive but all you can manage is lying on the bed, then that maybe not so good either*" (P03, Australian woman aged 41–50)). Age appeared to be a factor in weighing these trade-offs ("*I'm still in my 30s, so I've still got so much more to live for and I still have the mental and physical strength really to endure a lot more*" (P01, Australian woman aged 31–40); "*I'm 82 and I don't think I could go with [chemotherapy] because my quality of life would be zero. If the effects were really bad, I would just say no and accept it*" (P13, Australian man aged ≥ 81)).

Affect management Many participants perceived that the emotional burden associated with information-seeking and vigilance outweighed any benefits these might confer to treating their disease. Instead, they focused attention on managing their affective response to uncertainty, which they perceived to fall more within their control.

Participants used a range of approaches to managing their emotional responses to mUM, with varying degrees of success. At least two participants talked about cultivating a continuing sense of awareness regarding their disease status that softened the disappointment of being reminded after temporarily forgetting, but this also meant they never fully enjoyed periods of normalcy that could provide respite ("*[there is] not an hour of the day that goes by where I don't somehow subconsciously think about what I have... [despite] getting comments all the time, 'you look fantastic - are you sure you're sick?'*" (P10, Canadian man aged 71–80)).

Most participants tried to stay "*positive*" (P01, Australian woman aged 31–40; P03, Australian woman aged 41–50; P04, New Zealand woman aged 61–70: P05, European woman aged 41–50; P07, Australian man aged 31–40; P09, Australian woman aged 51–60; P15, Australian woman aged 61–70) about how long their treatment might continue to be effective and "*not to dwell*" (P11, American man aged 71–80; P14, New Zealand woman aged 61–70 receiving treatment in Australia) on worst case scenarios. Some participants focused on the possibility that a new "*breakthrough in treatment*" (P04, New Zealand woman aged 61–70) might emerge in the meantime ("*I still pin my hopes that there's going to be something else better coming down the pipe. I keep telling my oncologist, 'keep me alive for another few years until they come up with the next best treatment' because we've got to keep marching on*" (P10, Canadian man aged 61–70)). The newness of treatment options for mUM was seized upon by some participants as evidence of innovation that might yield further breakthroughs. In the case of the woman who sourced her own information, this was buoyed by a belief that people had been recently cured ("*til ipi-nivo, basically it was not treatable or not curable. And now so many are cured with this double immunotherapy. So it just needs a treatment or a combination. And then suddenly the odds look different*" (P05, European woman aged 41–50)).

Another affective management strategy involved relinquishing control and taking a fatalistic approach. This was manifest in statements highlighting the unlikely chance of being diagnosed with such a rare disease and contextualising this within the broader unpredictability of life to place muM-related uncertainty into perspective ("*we are [all] supposed to die one day... I could cure the cancer with all the things I do and then get hit by a car the next day*" (P05, European woman aged 41–50); "*I'm 70. I will die sooner or later. We all will*" (P06, Swedish woman aged 61–70)). At least one participant demonstrated awareness that this form of reasoning was driven more by its potential for emotional benefit than the probabilities involved ("*at this moment in time, I think probably my chances of getting hit on my bike is probably less than my chances of coming to grief with the uveal melanoma, in fairness*" (P02, British man aged 51–60)). Many participants emphasised that they considered themselves "*lucky*" (P10, Canadian man aged 61–70; P12, British man aged 41–50) or "*grateful*" to be eligible for a particular treatment, any tumour response that followed, and less-than-expected side-effects ("*I'm really, really grateful to be alive*" (P05, European woman aged 41–50); "*so, boy, talk about odds. You can say, well, five in a million chance of getting ocular melanoma, but what are the odds that I would qualify for this treatment? What are the odds that I'm responding to this treatment? I'm probably responding to it as well as you could want. So how lucky is that? You've got to go with those positives or else it'll drive you nuts*" (P10, Canadian man aged 71–80)).

Our findings appeared to support Mishel's reconceptualization of some aspects of her theory to account for longer-term changes in worldview required after living with illness-related uncertainty for a prolonged period. Participants described learning to live with uncertainty as a process that was difficult to begin with but became easier over time as they re-oriented to living "*one day at a time*" (P03, Australian woman aged 41–50; P04, New Zealand woman aged 61–70) or "*in the now*" (P01, Australian woman aged 31–40), focusing on aspects of their life still within their control rather than worrying too much about the future ("*I had a hard time, sort of six months, I was thinking a lot. But then I realized that I'm living now [and] I must continue to live... so I think mentally, I'm quite stable right now. But initially it was a hard time*" (P06, Swedish woman aged 61–70); "*I don't tend to look too much into the future about that stuff, but*

I think that is how I try and keep things as normal as possible and control what I can control while I'm here" (P07, Australian man aged 31–40)). Some participants were even able to derive positive meaning from their experience by shifting their worldview to accommodate a new sense of perspective and prioritisation brought by cancer ("*I'm still making goals and achieving them.... I worked on [writing a book] on and off for 25 years. But I got the hard part done between the time I was diagnosed and we got them printed up about a year ago*" (P11, American man aged 71–80)).

E.Buffering

'Buffering' is a term used by Mishel to suggest that people might sometimes try to cope with uncertainty by ignoring new information that contradicts their ability to derive opportunity from it.

This strategy was evident in avoidant behaviours, such as cancelling a scan ("*I just didn't want to get that scan. I even cancelled the appointment... because you can tell yourself everything until it's black and white*" (P05, European woman aged 41–50)). A small number of participants also reported actively avoiding thinking forward to a time when treatment options might be exhausted ("*I never actually thought about it, to be honest. Just trying to stay positive*" (P04, New Zealand woman aged 61–70)). However, two participants appeared able to temporarily cordon off mental space to engage in advance care planning that would help their family cope from a practical perspective after their death ("*look, it's always distressing talking about it, but I think practically there are things that need to be talked about*" (P03, Australian woman aged 41–50); "*I'm the one who pays all the bills and I arrange that they will be paid automatically. So that will ease the initial problems for my husband*" (P06, Swedish woman aged 61–70)). After this task was completed, participants were able to return to positive thinking that excluded contemplation of their approaching end of life.

Discussion

Findings from the current study confirm and further elucidate Mishel's (1988, 1990) [10, 11] theoretical framework of perceived uncertainty in illness as applied to the perspectives of patients with mUM in the era of immunotherapy and targeted treatments. Our results suggest that clinician-patient communication should seek ways to foster patients' sense of control beyond their illness and enable them to manage meta-cognition in ways that maintain emotional wellbeing whilst also realistically appraising their prognosis. Supportive care may be especially needed in the lead-up to scans, and efforts should be made to communicate results to patients as quickly as possible afterwards. Some people with mUM may also benefit from help with discussing their prognosis and its implications with family and friends.

While many of our findings replicate those of previous qualitative research on uncertainty in people with advanced cancer receiving immunotherapy and targeted treatments [9], application of Mishel's framework additionally identified meta-cognition to be a key coping strategy with implications for supportive care. This is consistent with established communication guidance within the specialty of palliative care that aims to help patients 'hope for the best while preparing for the worst' [26]. After anti-cancer treatment fails, palliative care clinicians support patients to refocus their hope from lengthening survival to making the most of the time they have left through establishing priority-driven goals that will maximise their quality of life, documenting wishes for end of life care and appointing surrogate decision-makers in the event they lose capacity, and 'tying up loose ends' with regard to relationships and practical matters that confer a sense of completion and safeguard their family's future wellbeing after they have died. Our findings suggest that re-orientation of this kind should not be a postponed until treatment options have been exhausted [27]. Consistent with previous research [28], we found that people with advanced cancer can find planning for end-of-life empowering rather than detrimental to hope. However, clinicians initiating such conversations need to ensure they are iterative and tailored to the individual, enabling time to reflect and discuss with family [29]. Evolving psychotherapeutic techniques for people with advanced cancer on novel treatments are finding ways to combine approaches that simultaneously help people to maximize their enjoyment of life and plan around a limited prognosis [30].

Mishel's theory posits that illusion may not always be maladaptive but does not specify the mechanism by which it might be protective. To the best of our knowledge, our study is the first to suggest that some participants are skilled at using meta-cognition– alluded to as 'tricking' or 'fooling' themselves - to manage inconsistency between accepting their limited prognosis and hoping for a cure which might otherwise lead to negative affect referred to as dissonance in the psychological literature [31]. Our research confirms Mishel's theory that– when illness is life-threatening– emotional coping is enabled by leveraging the opportunity afforded by doubt [9, 13]. However, our participants appear to have gone one step further by actively exaggerating and harnessing uncertainty to increase hope. Participants in our study capitalised on both sources of uncertainty identified by philosophers– aleatoric (indeterminacy) and epistemic (lack of knowledge)– the randomness and uncontrollability of events, and inexplicable variability in treatment response. In each case, they inflated small parameters of doubt to downsize implications of their illness within the context of other vagaries of life, and exaggerate the likelihood of extending life through an imminent medical breakthrough or lifestyle factors. The rarity of mUM and newness of treatments appeared to increase opportunities for leveraging each source of uncertainty respectively– i.e., if someone can get a disease as rare as mUM then why can't other events occur of similarly low probability? And if tebentafusp emerged so recently then why not other, even more effective treatments in the near future?

Not all the participants in our study demonstrated meta-cognition. Many focused their coping strategies overwhelmingly on staying positive at the expense of planning for treatment failure. In quantitative research, denial has been associated with poorer mental health outcomes for people with cancer [32]. This has been supported by a previous qualitative study with bereaved carers of patients with metastatic cutaneous melanoma, which found that they regretted over-emphasising hope during immunotherapy because it left them ill-prepared for a sudden and late transition to end-of-life care [33]. This study and another focused on patient perspectives on metastatic cutaneous melanoma [34] mirrored our own in finding that some participants reported having received limited prognostic information from their medical teams. Our study had no way of verifying these claims, establishing or whether such information was given but not understood. However, other research suggests that oncologists may avoid discussing prognosis because they lack confidence in their communication skills, worry about destroying patient hope, or do not want to deal with patient distress [5]. Moreover, even oncologists who do discuss prognosis may over-emphasise the chance that outcomes will be positive either to avoid distressing patients, because of cognitive bias from encounters with exceptional responders, or because their own emotional wellbeing depends on them thinking wishfully.

Our findings follow others in highlighting the need to foster patients' sense of control wherever possible to compensate for the profound disempowerment people experience from cancer [35]. Consistent with Bandura's (1977) theory of self-efficacy [36], participants appeared more likely to engage in active rather than avoidant coping if they perceived that they could take an influential role. Those who were coping well appeared to benefit from simultaneously 'letting go' of control over their prognosis [37] and refocusing their sense of control on their affective response to uncertainty. It may be that this dual-pronged psychological approach can be fostered in patients whose default is to become avoidant through a combination of acceptance commitment and cognitive-behavioural approaches [38, 39]. Recent research suggests that even 'scanxiety'– which featured prominently in our interviews and other qualitative and survey research with people with cancer across tumour types and stages [9, 40–42]– may be ameliorable by reframing scans as a means of exerting control over planning for the future [43]. Patients can also be encouraged to exert control through lifestyle changes that will improve their fitness for treatment, whilst also emphasising that there is limited evidence for exercise and diet treating cancer directly [44].

An obvious way to enhance sense of control in many cancer contexts is to give patients a more active role in treatment-related decision-making. However, decision-making for mUM may be less empowering than for some other cancers because treatment options are so limited and epistemic uncertainty reduces the degree to which decisions can be informed. As in previous studies, we found participants varied in their preferences for involvement in decision-making from those who wanted to take a leading role, through those who wanted a more shared approach to those who preferred their medical teams to make the decision on their behalf [45, 46]. Intuitively, a trusting therapeutic alliance with the medical team might be considered most important for patients with more passive decision-making preferences. However, our findings underscore the need to also build trust with patients who prefer a very active role to ensure that communication pathways remain open regarding their efforts to find information through social networks and social media. In such cases, efforts should be made to support feelings of control that patients may gain from information seeking whilst also monitoring for and tactfully addressing misinformation.

Our findings on clinical trials mirror those of a recent meta-synthesis of other qualitative studies in cancer patients [47], which found that patients' primary motivation to participate is to access new treatments. Some participants in our study appeared to misunderstand fundamental tenets regarding the differences between early versus late phase trials, equipoise and randomisation, and even to be unsure about whether they were enrolled on a clinical trial, highlighting the need to check for understanding when collecting informed consent.

Limitations

Our study has several limitations. Most importantly, its cross-sectional design precludes an understanding of how differing coping strategies may change over time and influence psychological outcomes in the event of treatment failure and transition to end-of-life care. Our approach to recruitment may have biased sampling towards people more willing to discuss their response to uncertainty, and so under-represented people for whom treatment was unsuccessful and/or had an avoidant coping style. Most people in our sample presented as well-educated and had close supportive relationships, which have been shown to correlate with more positive coping [48]. Higher education levels might have meant our sample were more likely than average to seek information about disease and treatment from sources other than their medical teams. Whilst mUM presents a prototypical example that can inform support for people with other tumour types receiving similar treatment developments in the future, the transferability of our findings is limited by the unusually low symptom burden associated with mUM which enabled many participants to forget they were ill for periods between medical appointments. Our analysis was constrained by our predominantly deductive approach using Mishel's framework, and may have missed insights that would have arisen from using other coping frameworks favoured by previous studies of emotional responses to cancer [49], or a more inductive approach. However, researchers' lack of familiarity with Mishel's framework at the inductive stage of analysis makes it unlikely they were influenced by knowledge of its components. Sample size was determined by information power for describing the range of quality-of-life issues reported by participants rather than in-depth exploration of uncertainty in particular. Our data yielded findings relevant to all components of Mishel's framework except cognitive capacity. Possible reasons this component did not appear to play a role for our sample include the following: cognitive capacity to provide informed consent was an eligibility criterion; participants were relatively young compared to most cancer patients and did not have brain metastases; immunotherapy and targeted therapies are less strongly associated with 'brain fog' than chemotherapy. Finally, while the research team included clinical members, the analysis was primarily undertaken by a social scientist with no clinical experience of delivering supportive care to people with cancer facing uncertainty.

Conclusion

This study offers new insights informative to supportive care for people with mUM aimed at enhancing their coping with uncertainty in the era of immunotherapy and targeted treatments. Head-to-head comparisons are needed of different approaches to supporting emotional wellbeing within the context of realistic communication about prognosis, which will enable people with mUM to hope for the best while preparing for the worst.

Abbreviations

mUM	Metastatic uveal melanoma

Supplementary Information

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Supplementary Material 1

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Author contributions

TL, CN, JL, DK, BM, AJ contributed to the study conception and design. Data collection and analysis were performed by TL and CN. The first draft of the manuscript was written by TL, and CN, JL, DK, BM, AJ commented on subsequent versions of the manuscript. TL, CN, JL, DK, BM, AJ read and approved the final manuscript.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due to the risk of re-identifying participants from whole transcripts.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the St Vincent's Hospital Sydney Human Research Ethics Committee (2022/ETH01013, approved 9th June 2022). Informed consent was obtained from all participant involved in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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