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Review article

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Advances in the clinical management of uveal melanoma

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Abstract

Melanomas arising in the uveal tract of the eye are a rare form of the disease with a biology and clinical phenotype distinct from their more common cutaneous counterparts. Treatment of primary uveal melanoma with radiotherapy, enucleation or other modalities achieves local control in more than 90% of patients, although 40% or more ultimately develop distant metastases, most commonly in the liver. Until January 2022, no systemic therapy had received regulatory approval for patients with metastatic uveal melanoma, and these patients have historically had a dismal prognosis owing to the limited efficacy of the available treatments. A series of seminal studies over the past two decades have identified highly prevalent early, tumour-initiating oncogenic genomic aberrations, later recurring prognostic alterations and immunological features that characterize uveal melanoma. These advances have driven the development of a number of novel emerging treatments, including tebentafusp, the first systemic therapy to achieve regulatory approval for this disease. In this Review, our multidisciplinary and international group of authors summarize the biology of uveal melanoma, management of primary disease and surveillance strategies to detect recurrent disease, and then focus on the current standard and emerging regional and systemic treatment approaches for metastatic uveal melanoma.

Sections

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Key points

- Advances in the understanding of the biology and immune microenvironment of uveal melanoma have improved prognostication and led to promising therapeutic strategies being tested in the adjuvant and metastatic settings.
- Stratification of patients by risk of metastatic disease following treatment of primary disease using anatomical, clinical and molecular features has enabled the development of individualized radiographic surveillance strategies.
- Tebentafusp, a first-in-class Immune-mobilizing monoclonal T cell receptor Against Cancer (ImmTAC), is the first therapy demonstrated to improve overall survival in patients with advanced-stage uveal melanoma.
- The successful development of tebentafusp highlights the clinical efficacy that can be achieved with appropriate modulation of the antitumour immune response in this disease historically considered immune-resistant.
- Novel regional therapeutic strategies focused on uveal melanoma liver metastases, systemic targeted, epigenetic and immunological treatments, and combinatorial approaches are being studied, providing hope for continued progress.
- Advances in the metastatic setting are driving the development of novel adjuvant therapies that might reduce the risk of metastatic spread and increase cure rates for patients with uveal melanoma.

Introduction

Uveal melanoma is a malignancy deriving from extracutaneous melanocytes residing within the uveal tract of the eye, with 90% of cases arising in the choroid, 6% in the ciliary body and 4% in the iris[1]. The annual incidence of uveal melanoma varies globally, partially owing to its more common occurrence in non-Hispanic white individuals when compared with Hispanic, Asian or Black individuals[2]. In Europe, the age-standardized incidence of the disease increases from south to north, with <2 cases per million persons in Spain and southern Italy and >8 per million in Norway and Denmark[3]. The age-adjusted incidence is 5.2 cases per million individuals in the USA and 7.2 per million in Australia[4,5]. Unlike in cutaneous melanoma, however, ultraviolet light is not implicated in the pathogenesis of uveal melanoma[6,7], with the exception of iris melanomas, which arise from a region of the eye exposed to sunlight[8]. Nevertheless, shared risk factors exist, including the presence of common and atypical cutaneous naevi, fair skin colour, a propensity to sunburn, light eye colour and iris naevi[9], suggesting that one or more genomic determinants of cutaneous pigmentation, such as select polymorphisms of *MC1R* (encoding melanocortin 1 receptor, a G protein-coupled receptor that regulates mammalian skin and hair colour) might increase the risk of melanocyte transformation independent of pigmentary pathways[10]. Indeed, melanocortin 1 receptor has been demonstrated to have crucial roles beyond determination of skin pigmentation, including effects upon DNA damage and repair, cell cycle control and apoptosis[11,12]. Additional shared risk factors include occupational exposures associated with cooking and welding[9]; however, the precise nature of the causative agent, whether it be ultraviolet or other non-ionizing radiation, fumes (which can contain carcinogens) or radioactive materials, is not known. The presence of ocular or oculodermal melanocytosis (a congenital condition characterized by hyperpigmentation of the uveal tract, sclera and episclera), or of a melanocytoma (typically benign pigmented tumours of the optic nerve and uveal tract), has been observed in patients diagnosed with uveal melanoma[13,14]. Individuals with oculodermal melanocytosis have an estimated lifetime risk of developing uveal melanoma of 1 in 400 (0.25%)[15], whereas malignant transformation of melanocytomas is estimated to occur in 1–2% of affected individuals[14].

Between 2% and 5% of uveal melanomas are considered to be familial[16,17], most commonly associated with germline pathogenic variants of the tumour-suppressor gene *BAP1* (ref. 18). The point prevalence of uveal melanoma in individuals with germline *BAP1* mutations has been estimated to be 2.8%, with a lower median age at diagnosis in these individuals (50 years) than in an unselected population (63 years)[18]. Deleterious germline variants of *PALB2* (encoding partner and localizer of BRCA2, which is involved in homologous recombination repair of DNA double-strand breaks)[16], *MLH1* (encoding the DNA mismatch repair protein MLH1)[16], *SMARCE1* (encoding SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1, which is involved in transcriptional regulation as a component of the ATP-dependent SWI/SNF chromatin remodelling complex)[16], *NF1* (encoding neurofibromin 1, a GTPase-activating protein that negatively regulates RAS activity)[19] and *MBD4* (encoding methyl-CpG-binding domain protein 4, a glycosylase involved in base-excision repair of DNA damage)[20,21] are also implicated as susceptibility genes.

The vast majority of patients with uveal melanoma have disease limited to the eye at the time of diagnosis, with <3% having detectable distant metastasis at presentation[22]. Up to 87% of patients present with changes in vision or other ocular symptoms, with the remainder diagnosed incidentally during routine eye examination; approximately 8% are diagnosed after evolution of a previously identified presumed naevus[23]. Despite effective management of the primary lesion, 40–50% of patients with uveal melanoma ultimately develop distant metastases, most commonly involving the liver (93%), lungs (24%), bones (16%) and/or soft tissues (11%)[24]. Owing to the limited efficacy of available regional and systemic therapies, the historical median overall survival (OS) duration of these patient following clinical detection of metastasis has been around 1 year[25,26]. In January 2022, tebentafusp, a bispecific T cell-engager targeting CD3 and glycoprotein 100 (gp100) in an HLA-A*02:01-restricted fashion[27], became the first agent to receive regulatory approval for the treatment of metastatic uveal melanoma after an OS benefit over investigator's choice of therapy was demonstrated in an international phase III trial[28]. This advance has ushered in a new era of promise in the treatment of this disease.

Herein, we provide an overview of the biology of uveal melanoma, strategies used to manage localized disease, and approaches to risk stratification of patients and follow-up monitoring for disease recurrence. We then focus our discussion on the current and emerging regional and systemic therapies for metastatic uveal melanoma.

The biology of uveal melanoma

Unlike most other malignancies, the diagnosis of primary uveal melanoma is frequently made without histological assessment and based on clinical examination by slit-lamp biomicroscopy for tumours arising in the anterior segment (iris melanomas) or by indirect ophthalmoscopy for tumours within the posterior segment of the

eye (ciliary body and choroidal melanomas) alone. If enucleation is performed, the presence of histological features of the tumour that are associated with a poor prognosis, including extrascleral extension, involvement of the ciliary body, a high number of mitoses, epithelioid cell type, macrophage infiltration and closed vascular loops, can be assessed[29–31].

Uveal melanoma is characterized by recurrent oncogenic mutations and chromosomal copy number aberrations[6,32] (Fig. 1). Almost all cases harbour mutually exclusive mutations that occur early in tumorigenesis and lead to constitutive activation of the signalling pathway mediated by $G\alpha_{q/11}$-family heterotrimeric G proteins. The most common of these initiating mutations directly affect guanine nucleotide-binding protein G(q) subunit-α (GNAQ) or guanine nucleotide-binding protein subunit-α11 (GNA11), disrupting the intrinsic GTPase activity that is required for inactivation of these $G\alpha_{q/11}$ proteins[33,34]; however, activating alterations in cysteinyl leukotriene receptor 2 (CYSLTR2), a G protein-coupled receptor upstream of GNAQ and GNA11, or in phospholipase C-β4 (PLCβ4), which acts downstream of GNAQ and GNA11, are also observed[35,36] (Fig. 1). These mutations all result in activation of several downstream signalling cascades, including the mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)–protein kinase B (AKT) and YAP1 pathways[37–39].

An integrative analysis of 80 primary enucleated uveal melanoma specimens conducted as part of The Cancer Genome Atlas (TCGA) programme identified distinct genomic subgroups defined by chromosome 3 copy number as well as generally mutually exclusive alterations in the genes encoding BRCA1-associated protein 1 (*BAP1*), eukaryotic translation initiating factor 1A (*EIFA1X*), and splicing factor 3B subunit 1 (*SF3B1*) or other members of the spliceosome machinery such as serine/arginine-rich splicing factor 2 (*SRSF2*)[6]. Tumours with disomy of chromosome 3 (disomy 3) are associated with mutations in *EIF1AX* or *SF3B1*, whereas those characterized by monosomy of chromosome 3 (monosomy 3) frequently harbour alterations affecting the remaining copy of *BAP1*, which is located on chromosome 3, and therefore lack expression of BAP1 protein[6,40]. As discussed further below, these genomic findings have important prognostic implications; however, the mechanistic underpinnings of the differential patient outcomes require further study. For example, loss of BAP1 results in a broad

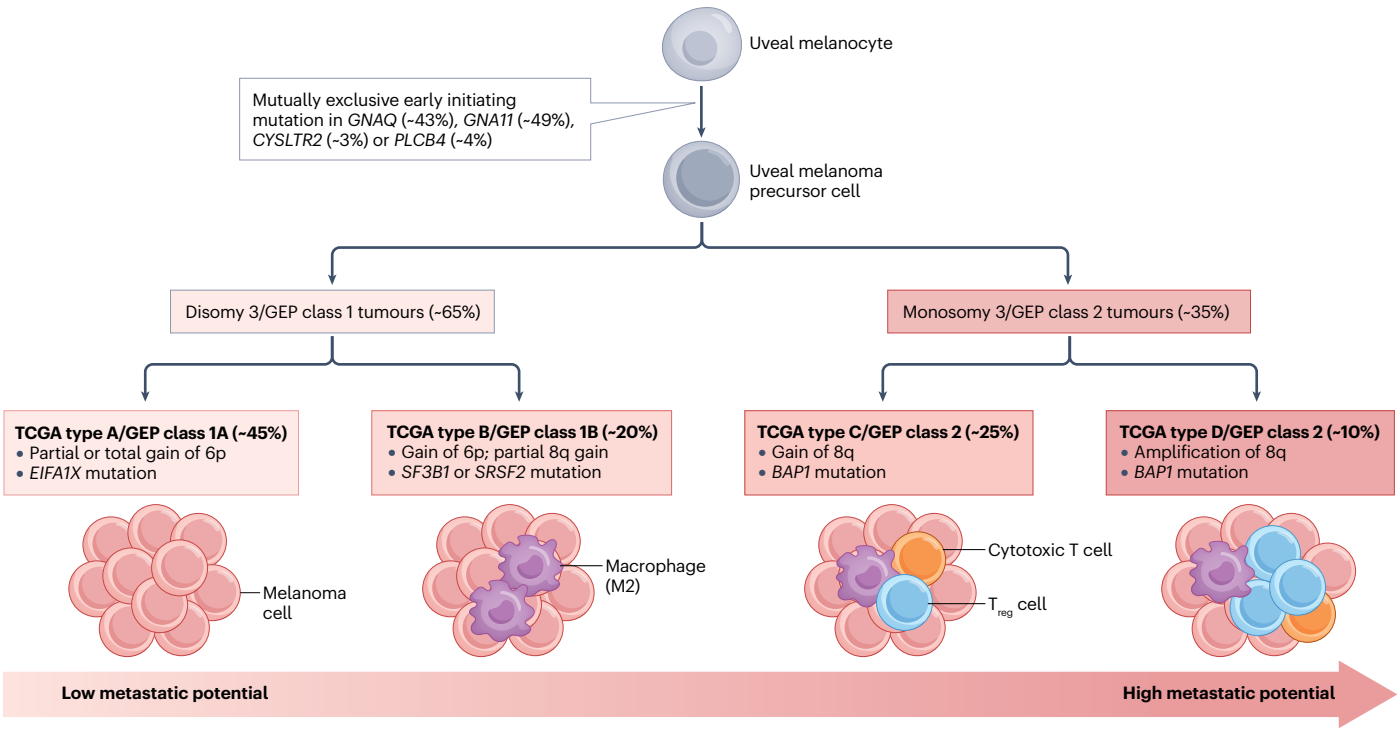

Fig. 1 | Evolution from uveal melanocyte to melanoma. The development of mutually exclusive mutations in *GNAQ*, *GNA11*, *CYSLTR2* or *PLCB4* in uveal melanocyte precursors can lead to the development of choroidal naevi and serve as early initiating alterations for the development of uveal melanoma. A pattern of subsequent recurring genomic events, which can be defined by specific cytogenetic, gene expression and/or mutational alterations, lead to malignant transformation, with tumour subtypes characterized by the different alterations having a variable capacity for distant metastasis. Uveal melanomas with disomy of chromosome 3 (disomy 3) are associated with a Decision-DX-UM class 1 gene expression profile (GEP) and have a generally favourable prognosis. The most favourable prognosis is observed for disomy-3 tumours harbouring mutations in *EIFA1X* and a class 1A GEP, correlating with the proposed The Cancer Genome Atlas (TCGA) type A subtype. These GEP class 1A tumours are typically devoid of infiltrating immune cells. Disomy-3 tumours harbouring gains of chromosome 6p, partial gains of chromosome 8q and mutations affecting components of the spliceosome machinery, most commonly SF3B1 or SRSF2, have greater metastatic potential than GEP class 1A tumours and are categorized as class 1B disease according to the Decision-DX-UM GEP classification and type B according to the integrative TCGA classification. An immune infiltrate predominated by tumour-associated macrophages can be observed in GEP class 1B tumours. Uveal melanomas with monosomy 3 correlate with GEP class 2 tumours and usually have *BAP1* mutation on the remaining copy of chromosome 3, resulting in loss of BAP1 expression, and are characterized by a metastatic potential that increases with chromosome 8q copy number. The TCGA classification further separates class 2 uveal melanomas into either type C tumours with three copies of 8q or type D tumours with more than three copies of 8q and characterized by a high number of infiltrating lymphocytes with a predominance of $CD4^+FOXP3^+$ regulatory T (T_{reg}) cells.

range of effects on chromatin architecture, transcriptional activity, DNA replication and repair, metabolic homeostasis, cell differentiation and other cellular processes[41], and the degree to which each of these changes affect the disease course is poorly defined.

In contrast to other malignancies, the presence of an inflammatory infiltrate in primary uveal melanomas is associated with a pro-tumour immune response and a poor prognosis[42,43]. Primary uveal melanomas with disomy 3 and BAP1 expression and without gains in chromosome 8q (the subset of tumours that frequently harbour *EIF1AX* mutations) commonly have minimal infiltrating immune cells, whereas those with disomy 3, BAP1 expression and gains in chromosome 8q (the subset commonly harbouring mutations in *SF3B1* or *SRSF2*) have a prominent macrophage infiltrate[44] (Fig. 1). Approximately 30% of primary tumours with monosomy 3 are characterized by an immune infiltrate containing T cells, including $CD8^+$ T cells, and $CD68^+$ macrophages[42,44,45], and express genes involved in the IFNγ signalling pathway (including *IFNG*, *IFMGR1* and *IRF1*), T cell-mediated cytotoxicity (*PRF1* and *GZMA*) and immunosuppression (*IDO1*, *TIGIT*, *CTLA4*, *PD1*, *Il6*, *Il10*, *FOXP3* and *LAG3*)[6], consistent with an active but restrained or exhausted antitumour T cell response. When T cells are present, a subpopulation of $FOXP3^+CD4^+$ regulatory T (T_{reg}) cells is typically observed[46], and infiltrating macrophages are predominantly of the pro-tumour M2 type[30,47], which is consistent with a tumour milieu in which T cells and macrophages are immunosuppressive and cytotoxic T cells are rendered dysfunctional.

The liver, by far the most common site of uveal melanoma metastasis, is characterized by an immunosuppressive environment maintained by liver-resident cells including Kupffer cells, hepatic stellate cells, dendritic cells, T_{reg} cells and liver sinusoidal endothelial cells. Hepatic metastases from uveal melanoma are enriched for $CD68^+CD163^+$ tumour-associated macrophages, which suggests an M2 phenotype that fosters tumour growth through promotion of angiogenesis and immunosuppression[48,49]. $CD4^+$ tumour-infiltrating lymphocytes (TILs) are present within these metastases, whereas $CD8^+$ TILs are more commonly located peritumourally, consistent with a cytotoxic T cell-excluded phenotype[48,50]. Immunological analysis of TIL cultures from 16 uveal melanoma liver metastases demonstrated a predominance of $CD4^+$ T cells, whereas cultures from 35 cutaneous melanoma liver metastases revealed a preponderance of $CD8^+$ TILs[51]. Although no difference in average $CD8^+$ T cell density was observed between uveal melanoma and cutaneous melanoma metastases, a substantially lower density of PD-1^+ T cells was observed in uveal melanoma lesions, suggesting that the infiltrating $CD8^+$ T cells have a naive phenotype[50]. $CD11b^+F4/80^+$ macrophage-mediated T cell elimination via activation of the FAS–FAS ligand pathway has been demonstrated in multiple mouse models of liver metastasis, suggesting one mechanism for the $CD8^+$ T cell exclusion[52]. In a molecular profiling study of 26 liver and six subcutaneous metastases from uveal melanoma, 'young TILs' generated from 15 HLA-A02:01-positive patients were, in eight patients, found to be potentially tumour-reactive (as demonstrated using MART1 dextramers or gp100 dextramers), but also prominently expressed the inhibitory immune-checkpoint receptors PD-1, TIM3, TIGIT and LAG3 (ref. 53). Notably, upregulation of the ligands for TIM3 and TIGIT in the setting of BAP1 loss was inferred based on evidence from preclinical experiments, suggesting an important mechanism of immune evasion in metastatic disease[53]. Additionally, expression of LAG3 and its ligands, particularly in the context of BAP1 loss, supports T cell exhaustion as a key mechanism facilitating tumour progression[54,55].

Management of localized uveal melanoma

Local treatment of the primary tumour

Local treatment of primary uveal melanoma has shifted over time from enucleation to eye-sparing modalities, based on results of the phase III Collaborative Ocular Melanoma Study (COMS) trial of enucleation versus iodine-125 episcleral plaque brachytherapy for small-to-medium-sized choroidal melanomas (apical height 2.5–10.0 mm and maximum basal tumour diameter ≤16.0 mm)[56]. This trial had a non-inferiority design and randomized 1,317 patients in a 1:1 ratio between the two treatment arms. With a minimum follow-up duration of 5 years, and 10–12 years of follow-up data for 799 patients, 5-year and 10-year all-cause mortality was 19% and 35%, respectively, in both arms, with a 10-year melanoma-specific death rate of 18% for those in the brachytherapy arm and 17% in the enucleation arm. By 12 years, the cumulative all-cause mortality was 43% with brachytherapy and 41% with enucleation. This study provided >80% power to conclude that neither treatment increases nor decreases mortality by up to 25% relative to each other, equating to a <5% absolute difference at 5 years and <10% at 10 years[56]. Despite the limitations of this study, including its conduct prior to the era of routine assessment of cytogenetic or molecular risk factors for patient stratification as well as limited duration of follow-up for mortality, brachytherapy is now accepted as a standard treatment for small-sized and medium-sized choroidal and non-choroidal tumours.

Importantly, in patients randomly assigned brachytherapy in the COMS trial, the Kaplan–Meier estimates for the risk of local treatment failure and of enucleation within 5 years were 10.3% and 12.5%, respectively[57]. The association between local treatment failure and reduced survival did not reach statistical significance (adjusted risk ratio 1.5; $P = 0.08$)[57]. However, an international, multicentre, retrospective analysis in 3,217 patients with ciliary body and choroidal melanomas treated with various modalities including, but not limited to, brachytherapy, enucleation or local resection, transpupillary thermotherapy or stereotactic radiotherapy, demonstrated that the 152 patients with local tumour recurrence had an increased risk of metastasis (HR 6.28, 95% CI 4.4–8.9; $P < 0.001$)[58]. Inferior outcomes have also been reported in patients with local recurrence of uveal melanoma following proton beam therapy[59,60].

Tumour resection can also be considered in highly selected patients such as those with small ciliary body or iris tumours (≤3 clock hours in size), although most patients with localized uveal melanoma are treated with various forms of radiotherapy, such as plaque brachytherapy or particle beam therapy, or with other ablative techniques, such as transpupillary thermotherapy or photodynamic therapy. Although the strength of available evidence is limited, OS has been reported to be similar in patients treated with enucleation and those treated with other therapeutic modalities, including cobalt plaque brachytherapy[61], proton beam therapy[62] and stereotactic radiosurgery[63]. Thus, selection of the primary treatment modality is dependent on both tumour-related and patient-specific factors, as well as local expertise. Enucleation should be considered for patients in whom the tumour has replaced >50% of the globe and/or resulted in blind painful eyes, as well as those who have extensive extraocular extension.

Risk stratification and prognostication

Although local disease control is achieved in >90% of patients presenting with localized uveal melanoma[64], the development of distant metastasis remains common, consistent with a predilection for haematological dissemination and establishment of occult micrometastases prior to primary tumour detection. Several clinical, histological and molecular factors are associated with the risk of uveal melanoma metastasis.

The American Joint Committee on Cancer (AJCC) classification system for uveal melanoma utilizes clinical features only (tumour size, presence of ciliary body involvement and/or extraocular extension, and clinical and/or radiographic regional or distant disease involvement), and includes a staging system for posterior tumours arising in the choroid or ciliary body, as well as a second separate system for iris melanomas, given their unique biology and clinical course (for iris melanomas only, the presence of glaucoma is also included in staging)[65–67]. Increasing AJCC stage, based on tumour size (largest basal diameter and thickness) as well as the presence of ciliary body involvement and/or extraocular extension, is strongly associated with the risk of metastasis, with 10-year metastasis-free survival (MFS) of 95% for stage I uveal melanoma decreasing to <60% for stage III disease[66]. Integrating various molecular tumour characteristics described below with AJCC stage has been demonstrated to enhance prognostication in patients with uveal melanoma[68,69].

DNA-based (cytogenetic and DNA sequencing) or RNA-based assays (gene-expression profiling), all of which require tumour biopsy samples, can also be used for prognostication (Table 1). Biopsy sampling should be considered for patients not undergoing enucleation, as recommended in national guidelines such as the National Comprehensive Cancer Network (NCCN) guidelines for uveal melanoma[70] and the Uveal Melanoma UK National Guidelines[71]; however, a balanced discussion of the potential risks and benefits of this procedure is necessary. Confirmation of diagnosis, molecular risk stratification, and implications for surveillance strategies and for clinical trial enrolment favour biopsy sampling, although the risks, including procedural complications, tumour seeding and inadequate tumour sampling, should also be considered[72,73].

DNA-based prognostication based on recurrent chromosomal changes is commonly performed in Europe, Asia, Australia and at certain centres in the USA and Canada. The most clinically significant cytogenetic alteration is monosomy 3, which is observed together with alterations in BAP1 in >80% of patients[6] and is associated with a large basal tumour diameter, epithelioid cellularity, ciliary body involvement, closed vascular loops, extrascleral extension, metastatic disease and uveal melanoma-related death[74–76]. The hazard ratio for MFS associated with loss of chromosome 3 is 3.2; however, other recurrent alterations, including polysomy 8q (HR 2.3) and/or loss of 8p (HR 1.97), 1p (HR 2.16) and 6q (HR 1.61), also connote increased metastatic risk[75,77,78]. In a study of patients who underwent enucleation (46.2%), proton beam radiotherapy (16.2%), brachytherapy (15.3%), transscleral resection (12.6%), endoresection (8.8%) or photodynamic therapy (0.9%), 10-year disease-specific mortality was 0% in 133 patients with disomy 3 tumours, 55% in 205 patients with monosomy 3 tumours without gain of chromosome 8q, and 71% in 168 patients with tumours harbouring both cytogenetic abnormalities[79]. Accordingly, assessment of chromosomal 3 and 8q copy number can be used to stratify patients into TCGA prognostic groups A to D, with 5-year MFS of 96% for group A disease (disomy 3 tumours without 8q gain), decreasing to 40% for group D disease (monosomy 3 tumours with 8q amplification)[80,81]. Cytogenetic testing can be performed with various different assays, such as fluorescence in situ hybridization (FISH), comparative genomic hybridization, single-nucleotide polymorphism arrays, microsatellite analysis (MSA) or multiplex ligation-dependent probe amplification (MLPA). Importantly, however, reported associations between cytogenetic findings and outcomes vary depending on the assay used, probably owing to differences in the patient populations tested, follow-up duration and test characteristics. For example, the reported 5-year MFS rates in patients with monosomy 3 detected using FISH-based and MLPA-based assays range from 40% to 60% and from 30% to 40%, respectively[82]. Prognostication with cytogenetics is enhanced when considered alongside AJCC tumour stage and other clinicopathological features[68,69]. The Liverpool Uveal Melanoma Prognosticator Online (LUMPO) tool integrates cytogenetics using an MLPA assay with anatomical, pathological and demographic factors for prognostication[83], and has demonstrated a generally good ability to discriminate between patients who died from uveal melanoma and those who survived in

Table 1 | Summary of risk stratification methods used in patients with uveal melanoma

Method	Tests	Risk groups	5-year MFS (%)	10-year MFS (%)	Considerations
AJCC 8th edition classification of uveal melanoma (primary ciliary body and choroidal melanomas)[66]	Clinical examination and/or pathological assessment	Stage I	97	94	Widely available and does not require biopsy of primary tumour Prognostic value is enhanced when incorporated with molecular features[68,69]
		Stage IIA	89	84	
		Stage IIB	79	70	
		Stage IIIA	67	60	
		Stage IIIB	50	50	
		Stage IIIC	25	NR	
Cytogenetics combined with clinical features[74,75,83]	Uveal Melanoma Prognostic Genetic Test or other cytogenetic assay results applied to LUMPO[a]	Individualized	Variable	Variable	Requires biopsy of primary tumour in patients not undergoing enucleation Test can fail (or produce equivocal result) if sample is insufficient
DNA sequencing[6,85,86]	Uveal Melanoma Prognostic Genetic Test, DecisionDx-UMSeq, or other institutional assays	*EIFA1X* mutant	100	90	Requires biopsy of primary tumour in patients not undergoing enucleation Test can fail (or produce equivocal result) if sample is insufficient
		SF3B1 mutant	85	55	
		BAP1 mutant	25	20	
Gene-expression profiling[90,91]	DecisionDx-UM	Class 1A	98	NR	Requires biopsy of primary tumour in patients not undergoing enucleation Test can fail (or produce equivocal result) if sample is insufficient. Financial reimbursement only available in North America
		Class 1B	79	NR	
		Class 2	28	NR	

AJCC, American Joint Committee on Cancer; MFS, metastasis-free survival; NR, not reported. [a]The Liverpool Uveal Melanoma Prognosticator Online (LUMPO) enables prognostication based on clinical features alone, without the inclusion of histological and cytogenetic data.

independent datasets (C-statistic, 0.72)[83]. Cytogenetic analysis using both MLPA and MSA, as well as DNA sequencing of *GNAQ*, *GNA11*, *SF3B1* and *EIF1AX*, is used in the commercially available Uveal Melanoma Prognostic Genetic Test[84].

DNA sequencing of primary uveal melanomas for recurrent genetic alterations also provides prognostic information, with 5-year MFS of 100%, 85% and 25% in patients with tumours harbouring *EIFA1X*, *SF3B1* and *BAP1* alterations, respectively[6,85,86] (Table 1). Testing of these genes is available commercially using the Uveal Melanoma Prognostic Genetic Test or DecisionDX-UMSeq[87], or can be performed using institution-specific sequencing assays[88].

DecisionDX-UM is a proprietary 15-gene expression profile test commonly performed in the USA that segregates uveal melanomas into class 1A low-risk tumours, class 1B intermediate-risk tumours and class 2 high-risk tumours[89], with 5-year MFS of 98%, 79% and 28%, respectively[90–95] (Table 1). In the TCGA study[6], the mRNA-based transcriptional patterns of this specific set of genes were compared with tumour chromosome 3 copy number and *BAP1* status. Tumours characterized by disomy 3 without loss of *BAP1* expression corresponded with DecisionDX-UM class 1 tumours, and tumours with monosomy 3 with loss of *BAP1* expression corresponded with DecisionDX-UM class 2 tumours[6,96]. *EIF1AX* mutations were associated with DecisionDX-UM class 1A tumours, *SF3B1* and *SRSF2* mutations with DecisionDX-UM class 1B tumours, and *BAP1* mutations with DecisionDX-UM class 2 tumours[6,96]. Although the DecisionDX-UM classification largely reflects the presence of these cytogenetic and prognostic mutations, it captures additional features. Importantly, although the aforementioned TCGA classification segregated disomy 3 tumours into two transcriptomic groups (A and B), no established correlation exists between these groups and the Decision-DX-UM class 1 subgroups.

Preferentially expressed antigen in melanoma (PRAME) is a melanoma-associated cancer/testis antigen that has emerged as an independent prognostic marker in patients with uveal melanoma[97], and is being further evaluated in the ongoing Collaborative Ocular Oncology Group 2 (COOG2) study. DecisionDX-UM class 1 tumours with minimal versus marked PRAME expression have 5-year actuarial rates of metastasis of 0% versus 38%[97]. Although PRAME expression is associated with the presence of *SF3B1* mutations[97], suggesting enrichment in DecisionDX-UM class 1B tumours, it is also expressed in up to one-third of class 1A tumours[98]. Additionally, elevated PRAME expression is associated with shorter time to metastasis and melanoma-specific mortality in patients with DecisionDX-UM class 2 tumours[99]. PRAME gene expression testing is commercially available with the DecisionDx-PRAME assay[100], although PRAME expression can also be assessed using non-proprietary reverse transcription PCR or immunohistochemistry assays.

Surveillance strategies

Radiographic surveillance following local treatment of primary uveal melanoma is driven by the marked hepatotropism of this disease and the ability of disseminated uveal melanoma cells to remain dormant for long durations, with the development of overt metastases occurring >15 years following initial diagnosis in some patients[101]. Thus, recommendations for radiographic surveillance include prolonged and relatively intensive protocols (Table 2). The liver is the first site of distant recurrence in most patients, and is the only distant organ involved in 53% of patients at the time of death[24,102]. Extrahepatic recurrence in the

Table 2 | Guidelines for disease surveillance following definitive local treatment of primary uveal melanoma

Estimated risk of distant metastasis	NCCN guidelines[70]		UK national guidelines[71]	
	Risk definition	Surveillance recommendations	Risk definition	Surveillance recommendations
Low	AJCC stage: T1 disease GEP: class 1A Cytogenetics: Disomy 3; gain of chromosome 6p Tumour genetics: *EIF1AX* mutation	Imaging to evaluate signs or symptoms as clinically indicated Consider surveillance imaging every 12 months	Not specified	None specified
Intermediate	AJCC stage: T2 or T3 disease GEP: class 1B tumour Tumour genetics: *SF3B1* mutation	Imaging to evaluate signs or symptoms as clinically indicated Consider surveillance imaging every 6–12 months for 10 years, and then as clinically indicated	Not specified	None specified
High	AJCC stage: T4 disease GEP: class 2 Cytogenetics: monosomy 3; gain of chromosome 8q Tumour genetics: *BAP1* mutation; PRAME expression	Imaging to evaluate signs or symptoms as clinically indicated Consider surveillance imaging every 3–6 months for 5 years, followed by every 6–12 months in years 6–10, then as clinically indicated	Clinical and/or pathological features: AJCC T3 or T4 disease ± ciliary body involvement ± presence of epithelioid cells ± closed connective tissue loops (also termed extravascular matrix loops) ± a high mitotic count (more than five mitoses per 40 HPFs) GEP: class 2 Cytogenetics: monosomy 3 ± polysomy 8q Miscellaneous: risk of death ≥30% at 5 years (that is, TNM 7th edition stage III (A, B or C) disease)	Lifelong 6-monthly surveillance. Advice must take into account the individual's risk weighed against the cost and resource implications of shorter scanning intervals as well as the possible psychological effects on the patient and the patient's family from more frequent (for example, 3-monthly) testing The choice of imaging modality currently reflects local practice access, and also whether or not to exclusively image the liver or include extrahepatic sites

AJCC, American Joint Committee on Cancer; GEP, gene-expression profile; HPFs, high-power fields; NCCN, National Comprehensive Cancer Network.

absence of liver metastases has been reported in 11–40% of patients who develop stage IV disease[102,103], and can involve the lungs, bones and soft tissue. Brain metastases have been reported in up to 5% of patients with stage IV uveal melanoma, with their development typically occurring late in the disease course[24,104].

Gadolinium-enhanced MRI of the liver, including diffusion-weighted sequences, has greater sensitivity and positive predictive value (67% and 95%, respectively)[105,106] than ultrasonography (sensitivity 14%, positive predictive value 100%)[107] for the detection of metastases, with more lesions identified by MRI than by CT[108]. [^{18}F] Fluorodeoxyglucose (FDG) PET–CT has a relatively low sensitivity for detecting liver metastases owing to poor lesion-to-background ratios of FDG uptake, susceptibility to respiratory motion artefacts and the variable FDG avidity of uveal melanoma metastases (sensitivity 41%, positive predictive value 100%)[105,109]. Surveillance with liver function tests is not recommended, owing to a low sensitivity (~15%) and limited added benefit over imaging[110,111].

Differences in the relative costs of imaging modalities, the risk of false-positive findings, local expertise and accessibility, and exposure to ionizing radiation, as well as limited data on their comparative efficiency have contributed to geographical differences in surveillance practices[112]. In patients with uveal melanoma who have a low risk of distant metastasis, such as those with T1 disease as defined by the AJCC, DecisionDX-UM class 1A tumours, tumours with disomy 3 without gain of 8q, or with *EIF1AX* mutations, recommendations include imaging to evaluate signs or symptoms when clinically indicated and consideration of surveillance imaging every 12 months (Table 2), highlighting the de-escalation of recommended surveillance strategies that is possible through anatomical or molecular staging. Given the lack of established clinical benefit for radiographic surveillance, as well as the associated financial toxicity and potential negative effect on quality of life, we would not consider routine surveillance imaging in the absence of signs or symptoms of recurrence in patients at low risk of recurrence, such as those with DecisionDX-UM class 1A PRAME-negative disease who have an estimated 5-year MFS of ≥98%[97].

In patients at intermediate or high risk of distant metastasis as defined by the NCCN[70], consistent with a 5-year MFS of ≤85% (Table 1), hepatic imaging with gadolinium-enhanced MRI or ultrasonography should be performed, if local expertise is available, for at least 10 years at variable intervals depending on the level of risk and/or time since initial diagnosis, or when clinically indicated (see Table 2 for details). Given the potential for extrahepatic involvement, chest CT imaging is also performed in such patients at some centres in the USA. If FDG PET is utilized, incorporation with contrast-enhanced CT imaging is recommended. Involvement of the pelvic region or brain as the first site of recurrence occurs in <1% of patients[24,104,113]; therefore, exclusion of these regions from routine imaging is reasonable in the absence of indicative signs or symptoms.

Options for adjuvant therapy

To date, three comparative and one non-comparative randomized study of adjuvant therapies (Bacillus Calmette–Guérin, dacarbazine, fotemustine, and sunitinib or valproic acid) have been performed in patients with mostly high-risk uveal melanomas, although no treatment has been proven to provide a clinical benefit over observation alone[114–117] (Table 3). One signal-seeking case–control study[118] and four single-arm trials[119–122] testing these and other adjuvant therapies, including IFNα2, ipilimumab and crizotinib, have also been published with no compelling evidence of activity observed (Table 3). Despite high expression of MET in uveal melanomas[123] and preclinical data demonstrating decreased tumour cell proliferation and migration following exposure to crizotinib[124], a selective small-molecule inhibitor of receptor tyrosine kinases including MET, ALK and ROS, no improvement in relapse-free survival (RFS) was observed in patients treated with this agent in the adjuvant setting (median 30.6 months versus ~32 months in a historical control group)[122]. However, several additional novel adjuvant strategies are being developed or are already the subject of clinical investigation (Supplementary Table 1).

The multitargeted kinase inhibitor sunitinib has been evaluated in the adjuvant setting owing to the high prevalence of KIT expression on uveal melanoma cells, and was found to be associated with improved OS in patients with high-risk disease in a retrospective case series when compared with a historical control group with the same risk factors (univariate HR 0.53, 95% CI 0.29–0.99; $P = 0.041$), particularly in those aged <60 years ($P = 0.004$ in multivariate analysis)[125]. In a prospective non-comparative study of adjuvant sunitinib for 6 months in a high-risk patient population, 18-month RFS was 76% and 2-year OS was 96%, meeting the prespecified primary end point of an improvement in 2-year OS from 70% to ≥85%[117] (Table 3). In the same trial, adjuvant treatment with valproic acid, a histone deacetylase (HDAC) inhibitor demonstrated to have antitumour activity in uveal melanoma models and to increase HLA class I expression[126,127], also met the efficacy end point, with an 18-month RFS of 62.8% and a 2-year OS of 90.7%[117]. Accordingly, adjuvant sunitinib is being further evaluated as a single agent and in combination with valproic acid with the duration of treatment extended to 12 months (NCT02068586)[117] (Supplementary Table 1). Notably, HDAC4 is a key target of BAP1, and quisinostat, a pan-HDAC inhibitor with potent activity against HDAC4, prevents the growth of *BAP1*-mutant uveal melanoma in preclinical models[128]; a clinical trial of adjuvant quisinostat in patients with DecisionDx-UM class 2 uveal melanoma is expected to begin accrual in 2023 (Supplementary Table 1) (J. Lutzky, personal communication).

In a pilot study of adjuvant ipilimumab in ten patients with DecisionDx-UM class 2 uveal melanoma, eight patients had no evidence of distant disease at 36 months[120]. Although these results are promising, their interpretation is limited by the small sample size and heterogeneity of primary tumour size in the treated patients. A single-arm phase II trial assessing combined immune-checkpoint inhibition with ipilimumab and nivolumab in the adjuvant setting in patients with high-risk uveal melanoma has completed accrual, with results anticipated in 2024 (NCT03528408; Supplementary Table 1). Given the efficacy of nivolumab plus relatlimab, an antagonistic anti-LAG3 antibody, in patients with metastatic cutaneous melanoma[129] and the expression of LAG3 and its ligands in uveal melanoma[54], this combination is also of interest, and an amendment to the aforementioned phase II trial to add an adjuvant nivolumab plus relatlimab arm is being planned (S. Rapisuwan, personal communication). With the OS benefit achieved with tebentafusp in patients with metastatic uveal melanoma[28], evaluation of this agent in HLA-A*02:01-positive patients in the adjuvant setting is of high priority. Although a study of adjuvant tebentafusp has not been initiated, the ongoing TebeMRD study is investigating the efficacy of this agent in the molecularly relapsed disease setting as defined by the presence of detectable circulating tumour DNA (NCT05315258).

Treatment of metastatic uveal melanoma

Current approaches

Despite a high suspicion for metastases when new lesions are identified during radiographic disease surveillance, biopsy confirmation is recommended. Uveal melanoma typically has a low mutational burden,

Table 3 | Completed clinical trials of adjuvant therapy in patients with uveal melanoma

Study	Study design	Key eligibility criteria	Treatments (number of patients)	Outcomes
Randomized studies				
McLean et al. (1990)[114]	Comparative phase II trial	Posterior uveal melanoma	Bacillus Calmette–Guérin intradermal (34) vs observation (79)	MSS 59% vs 70% (P = 0.60) after at least 5 years median follow up
Desjardins et al. (1998)[115]	Comparative phase III trial	LTD > 10 mm and tumour height > 5 mm	Dacarbazine (171) vs observation (177)	5-year OS: 71% vs 68% (NS)
Piperno-Neumann et al. (2017)[116]	Comparative phase III trial	LTD > 15 mm with extrascleral tumour extension and/or retinal detachment or LTD ≥ 18 mm, and/or monosomy 3 or partial deletion of 3p with 8q gain	Fotemustine (122) vs observation (122)	3-year MFS 60.3% vs 60.7% (HR 0.97, 95% CI 0.64–1.47; NS) 3-year OS 79.4% with no difference between the treatments
Seedor et al. (2022)[117]	Non-comparative phase II trial	Monosomy 3 and 8q amplification or DecisionDx-UM class 2 tumour	Cohort 1: sunitinib (45) or valproic acid (43) (each for 6 months); cohorts 2 and 3: ongoing (see Supplementary Table 1)	2-year OS 95.6% and 90.7% for sunitinib and valproic acid, respectively, with both arms meeting the prespecified primary end point (2-year OS ≥ 85%)
Single-arm studies				
Voelter et al. (2008)[119]	Phase II trial with a matched historical control group	Choroidal involvement, LTD > 20 mm, extrascleral tumour extension and/or tumour height > 15 mm	Intra-arterial fotemustine (22 vs 66 in control group)	Median OS 9 years vs 7.4 years in control group (P=0.50) 5-year OS 75% vs 56%
Lane et al. (2009)[118]	Case series with a matched historical control group	Age ≥ 65 years, LTD ≥ 15 mm, ciliary body involvement and/or extrascleral tumour extension	IFNα2a (121 vs 242 in control group)	MSS: rate ratio 1.02 (95% CI 0.68–1.50; P=0.91) OS: rate ratio 0.84 (95% CI 0.58–1.20; P=0.34)
Valsecchi et al. (2018)[125]	Retrospective cohort study with a matched historical control group	Monosomy 3 or DecisionDx-UM class 2 tumour	Sunitinib (54 vs 74 in control group)	Sunitinib associated with improved OS in patients aged <60 years (P=0.004)
Fountain et al. (2019)[120]	Single-arm phase I/II trial	DecisionDx-UM class 2 tumour	Ipilimumab (10)	36-month MFS 80%
Binkley et al. (2020)[121]	Single-arm phase II trial	≥20% monosomy 3 by FISH	Dacarbazine and IFNα2b (33 vs 29 'control' patients[a])	5-year MFS and OS 64% and 66%, respectively, compared with 33% and 37% for 29 'control' patients[a] (unadjusted P=0.05 and P=0.02 for MFS and OS, respectively; P=0.56 and P=0.92, respectively, when adjusted for risk factors)
Khan et al. (2022)[122]	Single-arm phase II trial with a synthetic control arm	DecisionDx-UM class 2 tumour and LTD ≥12 mm	Crizotinib (34 vs 64 in control group)	Median RFS 30.6 months (NS when compared with matched historical controls)

FISH, fluorescence in situ hybridization; LTD, largest tumour diameter; MFS, metastasis-free survival; MSS, melanoma-specific survival; NS, not statistically significant; OS, overall survival; RFS, relapse-free survival. [a]Patients who met eligibility criteria but declined study treatment.

with <20 non-synonymous coding mutations and up to two coding indels per primary tumour and less than one single-nucleotide substitution per megabase[130], suggesting epigenetic alterations as key drivers of disease progression. Up to 2% of uveal melanomas, however, are hypermutated owing to the presence of germline inactivating mutations in *MBD4* and somatic loss of the wild-type allele located on chromosome 3, and are typically responsive to immune-checkpoint inhibitors (ICIs)[20,21,131], supporting tumour profiling by next-generation sequencing at the time of disease recurrence. Furthermore, with the regulatory approval of tebentafusp in the USA and Europe, performing germline HLA typing at the time of recurrence is crucial to identify those who carry the HLA-A*02:01 allele and might, therefore, benefit from this therapy.

Substantial geographical variation exists in the management of patients with metastatic uveal melanoma depending on local expertise and practice patterns. Given that liver-only or liver-predominant disease recurrence is common, management considerations include locoregional therapies focused on the liver, systemic therapeutic approaches and combinatorial strategies. A meta-analysis of trials conducted between 2000 and 2015 demonstrated improved progression-free survival (PFS) and OS in patients receiving liver-directed regional therapies (median PFS 5.2 months, median OS 14.6 months) when compared with those managed systemically (median PFS 2.8 months, median OS 9.3 months), independent of prognostic characteristics[25]. Thus, in patients with liver-predominant disease, a locoregional treatment approach, alone or in combination with systemic therapy, should be used when feasible, particularly in those for whom tebentafusp is not an option. As the extent of extrahepatic disease increases, however, a greater benefit from effective systemic therapies over regional approaches might be expected.

Locoregional therapeutic options. Locoregional treatment strategies range from resection or ablation of oligometastatic sites of uveal melanoma recurrence to hepatic arterial approaches (Fig. 2a).

Metastasectomy can confer substantial clinical benefit in highly selected patients with a long interval from initial diagnosis to development of metastatic disease and a small number of lesions[132]. Resection of uveal melanoma liver metastases, either alone or in combination with microwave ablation[133], radiofrequency ablation[134] or hepatic arterial infusion chemotherapy (HAIC)[135], has been evaluated in several cohort studies, with a systematic review of the data demonstrating median OS durations of 10–35 months for surgically treated patients versus 9–15 months for those receiving systemic chemotherapy or best supportive care[136].

Hepatic arterial therapies capitalize upon the relative dependency of metastasis over the non-malignant liver on the hepatic artery for vascular supply, and include modalities such as HAIC[137], radioactive microsphere administration for selective internal radiation therapy (SIRT)[138,139], immunoembolization[140,141], transarterial chemoembolization (TACE)[139,142,143], and localized delivery of chemotherapy by isolated hepatic perfusion (IHP)[144] or percutaneous hepatic perfusion (PHP)[145]. A number of retrospective and single-institution prospective studies of these various modalities have been published, with clinical activity reported for all, although they are hampered by selection bias and thus unclear generalizability. The wide variability in clinical benefit reported across studies of identical treatment modalities highlights the heterogeneity of the patient populations enrolled as well as the operator-dependency in the treatment effects. For example, the reported objective response rates (ORRs) achieved with SIRT in prospective trials range from 10% to 38%, although reported PFS is more concordant at 4.9–6.6 months[138,139].

To date, five randomized clinical trials of regional therapy for uveal melanoma have been reported[137,139,140,144,145] (Table 4). A phase II study using a 'pick-the-winner' design randomly assigned 52 patients (1:1) to undergo immunoembolization using granulocyte–macrophage colony-stimulating factor or bland embolization. The ORR (primary efficacy end point) was 21.2% with immunoembolization and 16.7% with bland embolization, with median hepatic PFS, systemic PFS and OS durations of 3.9, 10.4, and 21.5 months, respectively, for immunoembolization and 5.9, 7.1 and 17.2 months for bland embolization[140]. More prominent pro-inflammatory cytokine production was observed in those undergoing immunoembolization, which was correlated with a longer time to extrahepatic metastasis. Elevated serum IL-6 and IL-8 levels at 1 h and 18 h, respectively, after embolization were significant predictors of longer systemic PFS ($P \leq 0.001$ for both)[140]. The European Organisation for Research and Treatment of Cancer (EORTC) 18021 trial randomly assigned 171 patients (1:1) to receive fotemustine delivered either intravenously or by HAIC and did not demonstrate improved OS with HAIC, despite improvements in terms of PFS and ORR[137]. Interim results for the first 40 of the planned 108 patients enrolled in the SirTac study, a randomized phase II trial of SIRT versus TACE using cisplatin, demonstrated an ORR of 5% in each arm but superior PFS in favour of SIRT[139] (Table 4).

The other two randomized trials compared IHP or PHP with best alternative care (BAC)[144,145] (Table 4). IHP is a one-time open surgical procedure during which the liver is isolated from the systemic circulation via cardiopulmonary bypass and catheters are placed in the hepatic arteries and the inferior vena cava, which enables high-dose hyperthermic chemotherapy to be delivered directly to the liver with minimal systemic circulation (Fig. 2b). A retrospective study of this approach in 34 patients with liver-limited metastases from uveal melanoma suggested an improvement in median OS from 12.3 months among the 30 longest survivors in a synthetic control cohort to 26.0 months with IHP[146]. In the phase III SCANDIUM trial, 93 patients with isolated uveal melanoma liver metastases were randomly assigned (1:1) to IHP or BAC; although the OS data were not mature at the time of initial disclosure, the ORR was 40% with IHP (including a complete response rate of 7%) versus 4.5% with BAC ($P < 0.0001$), and the median PFS duration was 7.4 months versus 3.3 months ($P < 0.0001$)[144].

PHP is a minimally invasive procedure involving percutaneous placement of a catheter into the hepatic arteries for chemotherapy infusion as well as a double-balloon catheter within the inferior vena cava, enabling collection of the hepatic venous outflow via fenestrations in the catheter between the balloons and subsequent extracorporeal drug filtration before the blood is reinfused into the patient (Fig. 2c). A phase III study of PHP delivery of melphalan (PHP-mel) versus BAC in 93 patients with unresectable hepatic metastases from cutaneous or uveal melanoma demonstrated an improvement in hepatic PFS, the primary end point of the study (median 7.0 versus 1.6 months; $P < 0.0001$)[147]. No OS benefit was observed, although 57% of patients randomized to BAC subsequently received PHP-mel, compromising this analysis[147]. The FOCUS trial was subsequently initiated as a phase III trial of PHP-mel repeated every 6–8 weeks for up to six treatments versus BAC in 144 patients with liver-dominant metastatic uveal melanoma[145]. Owing to accrual challenges, the trial was amended to a single-arm study with a primary end point of ORR. The ORR in the 91 patients treated with PHP was 33% (8% with a complete response), compared with 12% in 32 patients receiving BAC[145]. A significant PFS improvement was observed in favour of PHP (median 9.0 versus 3.1 months; $P = 0.0003$), with a trend towards improved OS (median 20.5 months versus 14.1 months)[145]. Although the responses achieved with IHP and PHP in these trials are remarkable, the complexities of these procedures are substantial, limiting widespread adoption. Furthermore, confirmation of an OS benefit is crucial.

Systemic therapies. Multiple systemic treatments have been evaluated in patients with metastatic uveal melanoma with limited, if any, efficacy generally observed. Most of these clinical studies have been non-randomized single-arm trials, with only eight randomized trials evaluating systemic therapy alone completed since 2000 (refs. 28,148–154) (Table 4). Single-agent and combination chemotherapies have mostly been ineffective in patients with metastatic uveal melanoma, with ORRs ranging from 0% to 8% with the alkylating agents dacarbazine or temozolomide and up to 10% with fotemustine[137,155–158].

A number of additional systemic therapeutic approaches have also been investigated, including agents targeting angiogenesis[149,154,158–161], various cell-surface proteins expressed in uveal melanomas (such as KIT[149,162,163], MET[154], IGF1R[164], glycoprotein NMB[165] and EGFR[166]) and components of the PI3K signalling pathway (including mTOR[167], AKT[151] and PI3K[168]), as well as strategies exploiting tumour nutritional dependencies on arginine[169], all with limited efficacy. MEK inhibition was observed to have preclinical efficacy consistent with the constitutive MAPK pathway signalling resulting from upstream activating GNAQ, GNA11, PLCB4 or CYSLTR2 alterations in uveal melanoma[170,171]. This finding led to three randomized clinical trials evaluating selumetinib, an allosteric inhibitor of MEK1/2, in patients with metastatic uveal melanoma. An initial phase II trial of selumetinib alone compared with dacarbazine or temozolomide and the subsequent phase II SELPAC trial of selumetinib alone compared with selumetinib in combination with paclitaxel both demonstrated statistically significant improvements in the primary end points of PFS in favour of selumetinib and selumetinib combined with paclitaxel, respectively[150,153]; however the phase III

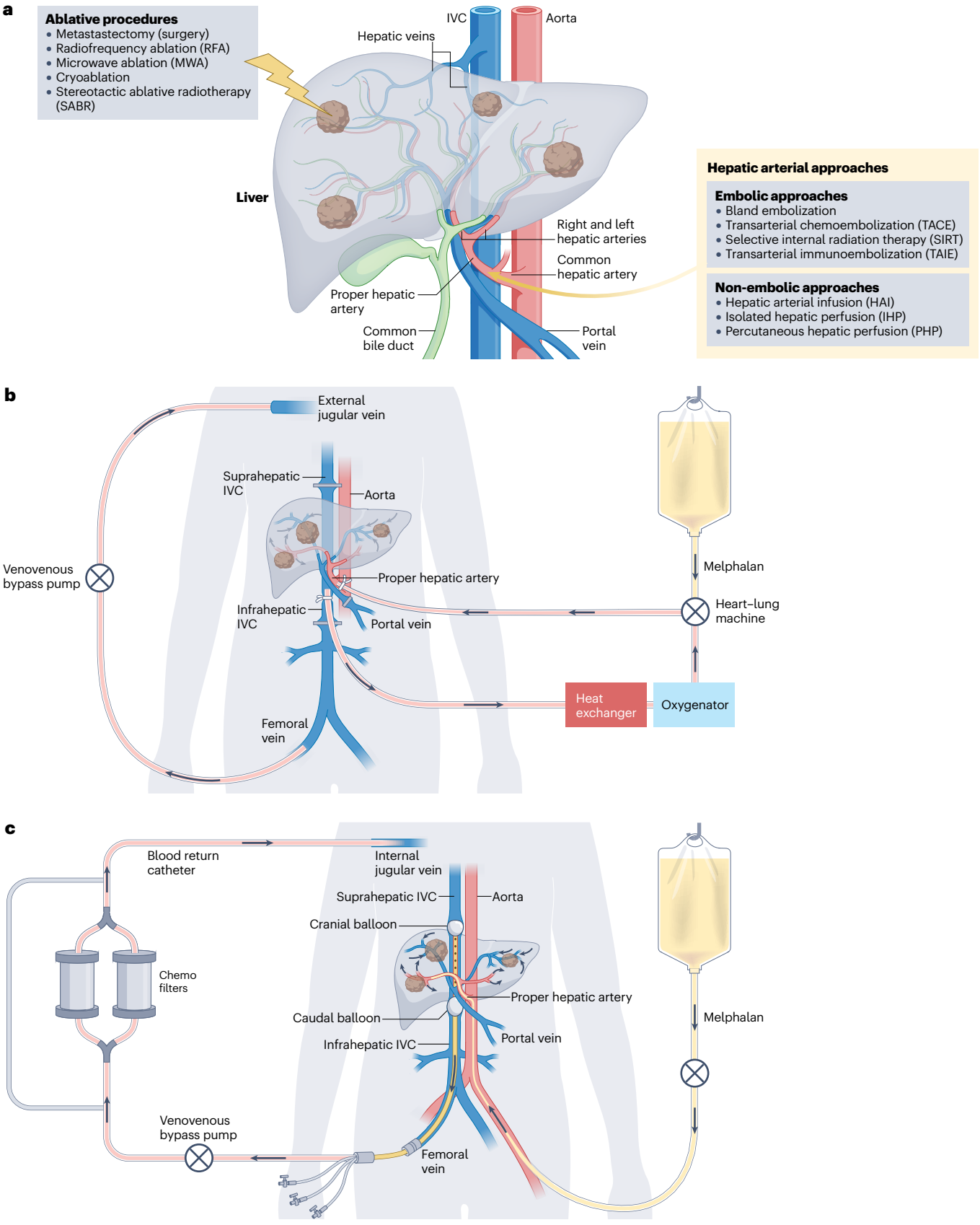
a
Ablative procedures
• Metastastectomy (surgery)
• Radiofrequency ablation (RFA)
• Microwave ablation (MWA)
• Cryoablation
• Stereotactic ablative radiotherapy (SABR)
IVC
Aorta
Hepatic veins
Liver
Right and left hepatic arteries
Common hepatic artery
Proper hepatic artery
Common bile duct
Portal vein
Hepatic arterial approaches
Embolic approaches
• Bland embolization
• Transarterial chemoembolization (TACE)
• Selective internal radiation therapy (SIRT)
• Transarterial immunoembolization (TAIE)
Non-embolic approaches
• Hepatic arterial infusion (HAI)
• Isolated hepatic perfusion (IHP)
• Percutaneous hepatic perfusion (PHP)
b
External jugular vein
Suprahepatic IVC
Aorta
Venovenous bypass pump
Proper hepatic artery
Infrahepatic IVC
Portal vein
Melphalan
Heart–lung machine
Heat exchanger
Oxygenator
Femoral vein
c
Blood return catheter
Internal jugular vein
Suprahepatic IVC
Aorta
Cranial balloon
Chemo filters
Proper hepatic artery
Caudal balloon
Portal vein
Infrahepatic IVC
Melphalan
Venovenous bypass pump
Femoral vein

Fig. 2 | Locoregional therapeutic options for liver metastases. **a**, Locoregional therapies for hepatic metastases include ablative procedures, such as surgical metastasectomy, radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation and stereotactic radiation therapy (SABR), as well as vascular approaches. Hepatic arterial embolic procedures include bland embolization, transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT), and transarterial immunoembolization (TAIE). Non-embolic approaches include hepatic arterial infusion (HAI) of chemotherapeutic agents, as well as isolated hepatic perfusion (IHP) and percutaneous hepatic perfusion (PHP). **b**, IHP is an open surgical procedure where the liver is isolated from the systemic circulation and perfused with melphalan under hyperthermic conditions. Laparotomy is performed allowing positioning of an inflow catheter in the proper hepatic artery and an outflow catheter in the infrahepatic inferior vena cava (IVC). These catheters are connected to a heart–lung machine and the liver is perfused with a high dose of chemotherapy, most commonly melphalan 3 mg/kg, as a one-time treatment lasting 60 min. **c**, PHP is performed under general anaesthesia and permits percutaneous isolation of the liver from the systemic circulation. A double-balloon catheter is inserted via the right common femoral vein and positioned in the IVC, with the cranial balloon in the right atrium–suprahepatic IVC junction and the caudal balloon in the infrahepatic IVC above the renal veins, and connected to an extracorporeal circulation system consisting of a centrifugal pump and an activated carbon drug filtration unit. After placement of the chemotherapy infusion catheter in the hepatic artery, melphalan is infused, and the effluent chemosaturated blood is aspirated through catheter fenestrations between the balloons of the double-balloon catheter and pumped through the filtration system to separate the melphalan from the blood. The blood is then returned to the systemic circulation through a sheath in the left internal jugular vein.

SUMIT trial of dacarbazine plus either selumetinib or placebo failed to demonstrated a significant difference in PFS (median 2.8 months versus 1.8 months; HR 0.78, 95% CI 0.48–1.27; $P = 0.32$)[152] (Table 4). No improvement in OS has been demonstrated with MEK inhibition in patients with this disease.

Despite the efficacy of ICIs in the setting of cutaneous melanoma, single-agent therapy with antagonistic anti-CTLA4 (refs. 172,173) or anti-PD-1 antibodies[174–176] has limited activity in patients with metastatic uveal melanoma. Efforts to enhance the efficacy of single-agent ICIs have included epigenetic strategies, which can upregulate the expression of immune signalling components in melanoma cells, prevent T cell exhaustion, induce chemokine expression and activate the innate immune system. PEMDAC was a phase II trial combining the HDAC inhibitor entinostat with the anti-PD-1 antibody pembrolizumab, and demonstrated an ORR of 14%, a median PFS duration of 2.1 months and a median OS duration of 13.4 months[177]. Results from two single-arm phase II trials of combined CTLA4 and PD-1 inhibition with ipilimumab and nivolumab, respectively, in patients with metastatic uveal melanoma have been reported, with both meeting the predefined criteria for success[178,179]. One of these trials (GEM-1402) included 52 patients with previously untreated metastatic uveal melanoma, and demonstrated a 12-month OS of 52%, a median OS duration of 12.7 months and an ORR of 11.5%[178]. The other trial (CA184-187) involved 35 previously treated or untreated patients, and showed a 12-month OS of 56%, a median OS duration of 19.1 months and an ORR of 18%[179]. Similar outcomes have been reported in retrospective series from both the USA and Germany[180,181]. However, the toxicity of this combination is substantial, with grade 3–4 immune-mediated adverse events (AEs) occurring in ≥40% of patients in the phase II trials[178,179]. The inferior clinical outcomes achieved with combination immune-checkpoint blockade in uveal melanoma relative to those observed in cutaneous melanoma probably reflect the low mutational burden[130], low level of intratumoural PD-L1 expression[182] and the immunosuppressive hepatic microenvironment[183] of the former tumour type. Nevertheless, ICIs have become a treatment option for patients with uveal melanoma in contemporary practice.

The development of tebentafusp is the most important therapeutic advance to date in the management of metastatic uveal melanoma. Tebentafusp is a first-in-class immune-mobilizing monoclonal T cell receptor against cancer (ImmTAC) that consists of a soluble affinity-enhanced HLA-A*02:01-restricted T cell receptor (TCR) specific for an epitope of gp100, a melanocyte lineage-specific antigen that is highly expressed on uveal melanoma cells, fused to single-chain variable fragment targeting the CD3 chain of the TCR complex on T cells. Thus, once bound to its specific peptide–HLA complex on the tumour cell surface, tebentafusp recruits and activates polyclonal T cells via their native TCR complexes to release cytokines and cytolytic mediators[27,184]. In the open-label phase III IMCgp100-202 trial, 378 HLA-A*02:01-positive patients with previously untreated metastatic uveal melanoma were randomly assigned (2:1) to receive tebentafusp or investigator's choice of pembrolizumab, ipilimumab or dacarbazine[28] (Table 4). Among the patients randomized to investigator's choice of therapy, 82% received pembrolizumab[28]. A significant improvement in OS was observed with tebentafusp: the estimated median OS duration was 21.7 months versus 16.0 months with investigator's choice of therapy and 1-year OS was 73% versus 59% (HR 0.51, 95% CI 0.37–0.71; $P < 0.001$)[28]. Despite this marked OS benefit, a more modest difference in PFS was observed with tebentafusp (median 3.3 months versus 2.9 months in the control group; 31% versus 19% at 6 months; HR 0.73, 95% CI 0.58–0.94; $P = 0.01$); the ORRs were 9% versus 5%[28]. The decoupling of radiographic response and OS benefit suggests the need for predictive biomarkers of benefit beyond radiographic assessment. In a single-arm phase II trial of tebentafusp, a significant linear relationship was observed between the level of circulating tumour DNA (ctDNA) reduction at week 9 and the hazard ratio for death ($R^2 = 0.9$; $P = 8.89 \times 10^{-7}$ by two-sided linear model), even in patients with a best radiographic response of progression, several of whom achieved complete ctDNA clearance[185]. Therefore, ctDNA is a biomarker of considerable interest. The most common treatment-related AEs observed with tebentafusp included cytokine-release syndrome resulting from T cell activation (any grade in 89% of patients; grade 3–4 in 1%) and skin-related events attributable to targeting of gp100-positive melanocytes (rash of any grade in 83% of patients; grade 3–4 in 18%)[28]. These toxicities decreased in incidence and severity after the first three or four doses[28]; however, observation for 16 h or longer during the first three courses of treatment is recommended to facilitate the management of cytokine-mediated hypotension.

Emerging therapeutic strategies

Novel approaches combining regional and systemic therapies, capitalizing upon tumour-intrinsic vulnerabilities or aiming to enhance the antitumour immune response are being developed to improve the outcomes in patients with metastatic uveal melanoma. A number of these strategies are the focus of ongoing and planned clinical trials (Supplementary Table 2).

Combined regional and systemic therapy. The safety and preliminary efficacy of administering ICIs concurrently with SIRT (NCT02913417), immunoembolization (NCT03472586) or IHP (NCT04463368) are

Table 4 | Randomized clinical trials of therapies for metastatic uveal melanoma conducted since 2000

Trial	Phase	Treatments (number of patients)	ORR (%)	Median PFS (months)	Median OS (months)
Regional (liver-directed) therapies					
SCANDIUM[144]	III	Isolated hepatic perfusion of melphalan (46) vs best alternative care (47)	40 vs 4	7.4 vs 3.3 ($P<0.0001$) Median hepatic PFS: 9.1 vs 3.3 ($P<0.0001$)	NR
SirTac[139]	II	Selective internal radiation therapy (20) vs transarterial chemoembolization using cisplatin (20)	5 vs 5	4.9 vs 2.2 ($P=0.037$) Median hepatic PFS: 8.3 vs 2.2 ($P=0.026$)	NR
FOCUS[145]	III	Percutaneous hepatic perfusion of melphalan (91) vs best alternative care (32)	35 vs 13	9.0 vs 3.1 ($P=0.0007$)	20.5 vs 14.1 (NS; *P* value NR)
Valsecci et al. (2015)[140]	II	Immunoembolization using GM-CSF (25) vs bland embolization (27)	21 vs 17	3.9 vs 5.9 (NS) Median hepatic PFS: 10.4 vs 7.1 (NS)	21.5 vs 17.2 ($P=0.047$ and $P=0.15$ for those with ≥20% and <20% liver involvement, respectively)
EORTC 18021 (ref. 137)	III	Hepatic arterial infusion of fotemustine (86) vs intravenous fotemustine (85)	10 vs 2	4.5 vs 3.5 months (HR 0.62, 95% CI 0.45–0.84; $P=0.002$)	14.6 vs 13.8 (HR 1.09, 95% CI 0.79–1.50; $P=0.59$)
Systemic therapies					
IMCgp100-202 (ref. 28)	III	Tebentafusp (252) vs investigator's choice of pembrolizumab, ipilimumab or dacarbazine (126)	9 vs 5	3.3 vs 2.9 (HR 0.73, 95% CI 0.58–0.94; $P=0.01$)	21.7 vs 16.0 (HR 0.51, 95% CI 0.37–0.71; $P<0.001$)
Alliance A091201 (ref. 154)	II	Cabozantinib (46) vs temozolomide or dacarbazine (9)	0 vs 0	1.9 vs 1.9 (HR 0.99; $P=0.96$)	6.4 vs 7.3 (HR 1.21; $P=0.58$)
SELPAC[153]	II	Selumetinib + paclitaxel (51) vs selumetinib (26)	14 vs 4	4.8 vs 3.4 (HR 0.61, 90% CI 0.41–0.92; $P=0.02$)	9 vs 10 (HR 0.98, 90% CI 0.58–1.66; $P=0.47$)
SUMIT[152]	III	Selumetinib + dacarbazine (97) vs placebo + dacarbazine (32)	3 vs 0	2.8 vs 1.8 (HR 0.78, 95% CI 0.48–1.27; $P=0.32$)	NR vs NR (at 37% maturity, HR 0.75, 95% CI 0.39–1.46; $P=0.40$)
NCI-2013-02091 (ref. 151)	II	Trametinib + uprosertib (21) vs trametinib (19)	5 vs 6	3.6 vs 3.6 (logrank $P=0.74$)	NR
NCI-2011-01411 (ref. 150)	II	Selumetinib (50) vs temozolomide or dacarbazine (51)	14 vs 0	3.6 vs 1.6 (HR 0.46, 95% CI 0.30–0.71; $P<0.001$)	11.8 vs 9.1 (HR 0.66, 95% CI 0.41–1.06; $P=0.09$)
SUAVE[149]	II	Sunitinib (38) vs dacarbazine (36)	0 vs 8	2.8 vs 3.9 (HR 1.09, 95% CI 0.62–1.92; NS)	6.4 vs 8.7 (HR 1.59, 95% CI 0.86–2.96; NS)
Schmittel et al. (2006)[148]	II	Gemcitabine + treosulfan (24) vs treosulfan (24)	4 vs 0	3.0 vs 2.0 (logrank $P=0.008$)	NR

GM–CSF, granulocyte–macrophage colony-stimulating factor; NR, not reported or not reached; NS, not statistically significant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

under investigation in patients with uveal melanoma. Moreover, the phase I PERIO-01 trial is evaluating intravascular pressure-enabled drug delivery of SD-101, a Toll-like receptor 9 agonist demonstrated to have activity when administered intratumourally together with pembrolizumab in patients with anti-PD-1 antibody-refractory cutaneous melanoma[186], into uveal melanoma liver metastasis, with or without systemic ipilimumab and/or nivolumab (NCT04935229). Regional pressure-enabled delivery is intended to enhance the penetration of SD-101 into the hepatic metastases in order to deplete liver-resident myeloid-derived suppressor cells and thereby promote a response to the systemic immunotherapy.

Targeting tumour-intrinsic vulnerabilities. Inhibition of PKC, a downstream component of the $G\alpha_{q/11}$ signalling pathway, results in suppression of uveal melanoma cell proliferation in preclinical models[187,188], and has led to several studies of sotrastaurin, an inhibitor of both conventional and novel PKC isoforms, in patients with uveal melanoma[168]. Despite the promising preclinical data, limited activity was observed in a phase I study of sotrastaurin alone in patients with treatment-naive metastatic uveal melanoma[189] or in combination with alpelisib[168], a selective inhibitor of the α-isoform of PI3K. Darovasertib is a next-generation PKC inhibitor with greater selectivity for the novel PKC isoforms and thus a toxicity profile distinct from that of sotrastaurin[190,191]. Encouraging activity was observed in a phase I trial of darovasertib, with six partial responses reported in 66 evaluable patients with metastatic uveal melanoma (ORR 9%)[190]. High levels of hepatocyte growth factor signalling impair the activity of darovasertib in preclinical models, and this antagonism can be overcome by concurrent treatment with crizotinib[192]. This strategy is now being evaluated in an ongoing phase I/II trial (NCT03947385), with preliminary data indicating a promising ORR of 31% in 35 evaluable patients with uveal melanoma[193]. At a median follow-up duration of 7.8 months, median PFS was approximately 5 months and the median duration of response had not been reached[193]. Grade 3 treatment-related AEs occurred in 9 of 37 patients, with no grade 4 or 5 AEs observed to date[193].

Constitutive $G\alpha_{q/11}$ signalling owing to *GNAQ* or *GNA11* mutations leads to dephosphorylation of YAP1 and TAZ, which are transcriptional co-activators involved in the Hippo signalling pathway, and promotes their oncogenic activity[194]. Focal adhesion kinase (FAK) is a crucial mediator of the YAP1 activation that results from *GNAQ* or *GNA11* mutation, and the antitumour efficacy of FAK inhibition has been demonstrated preclinically in models of uveal melanoma[195]. Additional studies in such models have demonstrated synergistic growth-inhibitory effects of concurrent MEK and FAK inhibition[196]. This preclinical work

has resulted in two ongoing clinical trials in patients with metastatic uveal melanoma, a phase I study of the FAK inhibitor IN10018 alone or in combination with the MEK inhibitor cobimetinib (NCT04109456) and a phase II study of the FAK inhibitor defactinib plus the RAF–MEK inhibitor VS-6766 (NCT04720417).

Additional targeted therapies for uveal melanoma are in early stages of development. YM-254890 and FR900359, both structurally similar macrocyclic depsipeptides, are pharmacological tools that allosterically inhibit GDP release from G proteins of the $G\alpha_{q/11/14}$ subfamily and prevent their activation by G protein-coupled receptors, resulting in diminished downstream signalling. FR900359 has been demonstrated to inhibit all oncogenic variants of $G\alpha_{q/11}$ found in uveal melanomas, with tumour growth inhibition demonstrated in cell line and xenograft models of this cancer[197,198]. Similarly, YM-254890 suppresses $G\alpha_{q/11}$ signalling and decreases uveal melanoma cell proliferation[199], slowing tumour growth but without inducing regression in xenograft models[200]. Notably, however, synergistic growth inhibition and tumour shrinkage was observed when YM-254890 was combined with a MEK inhibitor[200]. An innovative approach to targeting $G\alpha_{q/11}$ is being explored with the antibody–drug conjugate DYP688 (P. Yerramilli-Rao, personal communication). The safety, tolerability and preliminary efficacy of DYP688 are being explored in an ongoing phase I/II study in patients with metastatic uveal melanoma (NCT05415072).

IOA-244 is a highly selective non-ATP competitive PI3Kδ inhibitor that is being evaluated in a phase I study in patients with tumour types characterized by high levels of PI3Kδ expression, including uveal melanoma (NCT04328844). In mouse models, IOA-244 has been demonstrated to inhibit tumour growth alone and in combination with anti-PD(L)-1 antibodies, with decrease in T_{reg} cell and myeloid-derived suppressor cell populations[201].

Several epigenetic strategies are also being explored for the treatment of uveal melanoma. HDAC inhibition reverses the biochemical, transcriptomic and morphological consequences of BAP1 loss in preclinical models, resulting in tumour cell apoptosis and differentiation[126], potentially by disrupting the role of HDAC4 downstream of BAP1 (ref. 128), and synergizes with MEK inhibition[202]. Results from a completed phase II trial of the HDAC inhibitor vorinostat in patients with metastatic uveal melanoma are expected to be reported in 2023 (NCT01587352), and a phase II study of HDAC inhibitor belinostat combined with the MEK inhibitor binimetinib is ongoing (NCT05170334). The Brahma-associated factor (BAF) complex, an ATP-dependent chromatin remodelling complex that functions as both transcriptional activator and repressor, is another epigenetic target of interest. In uveal melanoma cells, melanocyte-lineage specific transcription factor recruitment to target genes is reliant upon chromatin remodelling by the BAF complex[203]. FHD-286 is a first-in-class inhibitor of BRM and BRG1, the ATPase subunits of BAF, that is being evaluated in a phase I study in patients with metastatic uveal melanoma (NCT04879017).

The *SF3B1* missense mutations that are present in ~20% of uveal melanomas result in aberrant utilization of alternative splice branch points and thus cryptic 3′ splice sites by the spliceosome, resulting in >1,400 non-canonical splice junctions and potentially enhanced immunogenicity owing to the generation of neoantigens[204]; however, the available clinical data do not demonstrate a clearly increased response to ICIs in this molecular subset of the disease[205]. Inhibiting methylation of arginine on histone or non-histone proteins mediated by protein arginine methyltransferases (PRMTs) induces cytotoxicity selectively in cancer cells harbouring mutations in splicing factors such as SF3B1 (ref. 206). Specifically, inhibition of PRMT5 results in downregulation of SF3B1 target genes such as *MBD4* and *BRD9* that are associated with increased retention of specific intron sites in a *SF3B1* mutation-dependent fashion[207]. Accordingly, several PRMT5 inhibitors, including PRT543 (NCT03886831), PRT811 (NCT04089449) and JNJ-64619178 (NCT03573310), are being tested in early clinical trials involving patients with uveal melanoma (Supplementary Table 2).

Enhancing the antitumour immune response. Continued exploration of immunotherapy strategies for uveal melanoma is crucial. Administration of autologous TILs harvested from uveal melanoma metastases, including those derived from the immunosuppressive hepatic microenvironment, has produced objective and durable tumour regression in 7 (35%) of 20 evaluable patients involved in a single-centre phase II study[208]. Notably, three of the responders had ICI-refractory disease[208]. Therefore, further evaluation of cellular therapies is warranted. Given the prevalence of LAG3 expression in uveal melanomas[54,55], a phase II trial of relatlimab plus nivolumab has been initiated, with accrual ongoing (NCT04552223; Supplementary Table 2). The MDM2 inhibitor alrizomadlin synergizes with anti-PD-1 antibodies by enhancing antitumour immunity, primarily via depletion of immunosuppressive M2 macrophages from the tumour microenvironment as a result of p53 activation and subsequent downregulation of MYC and MAF in these cells[209]. One of five patients with PD-1 inhibitor-refractory metastatic uveal melanoma had a partial response in a phase I/II study of the combination of alrizomadlin and pembrolizumab[210], with accrual to the uveal melanoma cohort ongoing (NCT03611868). Finally, given the clinical success of tebentafusp as well as the high level of PRAME expression in uveal melanomas[97], the ongoing development of IMC-F106C, an ImmTAC targeting a HLA-A*02:01-restricted epitope of PRAME, is of considerable interest. Preliminary results from the first-in-human phase I trial of this agent (NCT04262466) were recently presented at the ESMO 2022 Congress and included data from 11 patients with metastatic uveal melanoma, five of whom had previously received tebentafusp. Partial responses occurred in three of these patients and, interestingly, were restricted to those with tebentafusp-naive disease[211]. The safety profile of IMC-F106C was generally as expected based on its mechanism of action, with pyrexia and cytokine-release syndrome (which did not exceed grade 2) occurring in 64% and 45%, respectively, of all 55 patients treated.

Conclusions

The rising number of international collaborations, including the International Rare Cancer Initiative, UM CURE 2020, the Collaborative Ocular Oncology Group, EURACAN and others, has accelerated efforts aimed at elucidating the fundamental mechanisms contributing to uveal melanoma development, dissemination, dormancy and progression. Importantly, these efforts have resulted in a number of promising treatment strategies that are now being evaluated in clinical trials (Supplementary Tables 1 and 2). The generation and use of registry and real-world datasets would facilitate trial development and conduct, and would further document outcomes associated with the geographically varied practice patterns, provide additional information on the clinical course of distinct molecular subsets of the disease, and ensure that patient preferences and priorities are emphasized. The recent approval of tebentafusp is reflective of the collaboration in the field of uveal melanoma and provides a path for continued progress.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

R.D.C. has acted as a consultant for Alkermes, Aura Biosciences, Bristol Myers Squibb, Castle Biosciences, Chimeron, Delcath, Eisai, Hengrui, Ideaya, Immunocore, InxMed, Iovance, Merck, Novartis, Oncosec, Pierre Fabre, PureTech Health, Regeneron, Rgenix, Sanofi Genzyme, Sorrento Therapeutics and TriSalus Life Sciences; holds stock options in Aura Biosciences, Chimeron and Rgenix; and has received research funding through his institution from Amgen, Astellis, AstraZeneca, BioMed Valley, Bolt, Bristol Myers Squibb, Corvus, Cstone, Foghorn, Ideaya, Immatics, Immunocore, InxMed, Iovance, Merck, Mirati, Novartis, Pfizer, Plexxikon, Regeneron and Roche/Genentech. J.J.S. has acted as a consultant for Bristol Myers Squibb, Delcath, Immunocore and Merck Sharp & Dohme; has received speaker's honoraria from Pierre-Fabre and Immunocore; and research funding through his institution from AstraZeneca, Bristol Myers Squibb, Immunocore, Merck Sharp & Dohme and Replimune. D.J.E. has acted as a consultant for Delcath. R.O.B. has acted as a consultant for Amgen, BD/BARD, Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Roche and Sanofi Genzyme; has received speaker's honoraria from Pfizer and Roche; is a shareholder of SATMEG Ventures AB; and has received research funding through his institution from Bristol Myers Squibb and SkyLineDx. J.W.H. has acted as a consultant for Castle Biosciences and Immunocore; and receives patent royalties from Washington University. S.P.P. has acted as a consultant for Advance Knowledge in Healthcare, Bristol Myers Squibb, Cardinal Health, Delcath, Immunocore, Novartis and TriSalus Life Sciences; and has received research funding through her institution from Bristol Myers Squibb, Foghorn Therapeutics, Ideaya, InxMed, Lvgen, Novartis, Provectus Biopharmaceuticals, Seagen, Syntrix Bio and TriSalus Life Sciences. A.M.J. has received research funding through his institution from Ideaya and Immunocore. M.J.J., N.D.C. and S.P.-N. declare no competing interests.

Additional information

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