A SYSTEMATIC LITERATURE REVIEW OF TREATMENT OPTIONS FOR METASTATIC UVEAL MELANOMA

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Introduction

- Uveal melanoma (UM) is the most common primary intraocular neoplasm in adults, with a five-year overall survival (OS) rate of <50% (1). Treatments for primary UM are generally effective and locoregional spread is rare. Metastatic UM develops in up to 50% of cases (2) and spreads via the blood to the liver first in up to 95% of individuals followed by lung and bone (3). The extent of metastatic disease in the liver is an important determinant of clinical progression and survival (3). Most patients die from parenchymal liver failure (4).
- There are no systemic treatments for metastatic UM with a proven survival benefit and clinical guidelines frequently recommend patients are referred to clinical trials. Two recent meta-analyses published in 2019 examined a range of therapeutic approaches to metastatic UM including liver-directed therapies, systemic chemotherapies, immunotherapies, and targeted agents, demonstrating 12-month OS outcomes of 52-56% (5,6)
- A systematic literature review (SLR) of clinical trials for metastatic UM was performed, including randomised controlled trials (RCTs) and single arm trials.

Research Question

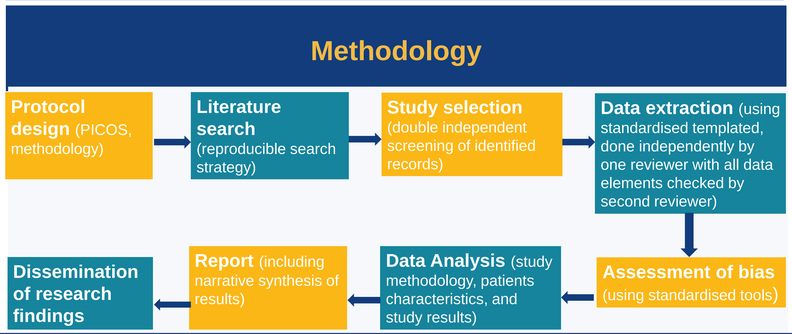
- What is the evidence for the efficacy and safety of treatments that may be considered for adult patients with advanced or metastatic UM?

Eligibility Criteria

Table 1. PICOS element: inclusion and exclusion criteria

Elements	Inclusion Criteria	Exclusion Criteria
Population	• Adult patients with advanced or metastatic UM or choroidal melanoma	• Patients with localised disease only; pediatric patients
Intervention	• Tebentafusp, IMCgp100	• Surgical interventions only
Comparator	• All other therapeutic interventions for CM/UM	• NA
Outcome	• Overall-survival (OS) • Progression-free survival (PFS) • Overall response rate (ORR) • Disease control rate (DCR) • Adverse events (AEs) • Quality-of-Life	• Outcome not listed in the “inclusion criteria” of PICOS
Study Design	• RCTs • Single arm trials • Conference abstracts • Studies comparing the intervention with a comparator or studies comparing two comparators	• Pharmacokinetic studies • Observational studies, editorials, and letters • Reviews/pooled trial analyses • Non-human and non-English studies

Methodology



Results – Study and Patients Characteristics

- 60 studies (11 RCTs and 49 single arm trials) reported in 80 documents were included (fig. 1, table 2)
- Three RCTs were phase III and eight were phase II trials.
- Total no of patients in RCTs ranged from 39 to 378
- Single arms trials were either phase I/II or phase II studies.
- For single arm trials, the number of patients ranged from 5 to 146.
- The mean age of patients ranged from 53–68 years
- 34% to 100% had liver metastases, 0% to 53% had lung metastases, 0% to 30% had bone metastases, 0% to 50% had cutaneous metastases and 0% to 6% had brain metastases.
- A wide gap (0 to 100%) in the percentage range of patients receiving previous treatments for UM or choroidal melanoma was observed.
- No patient in any study had a ECOG performance grade of ≥3.

Figure 1: PRISMA Flow diagram

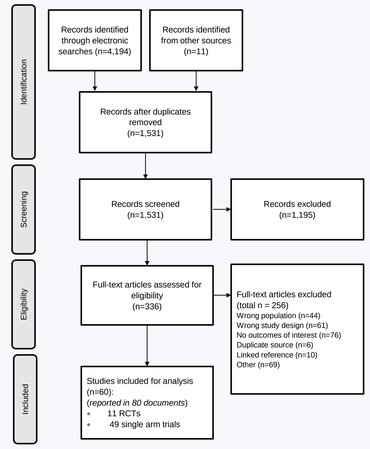


Table 2: Interventions assessed in at least one study arm of metastatic UM trials

Systemic therapies	
Chemotherapy (n=20)	• Bendamustine, cisplatin, carboplatin, dacarbazine, fotemustine, gemcitabine, nab-paclitaxel, paclitaxel, temozolomide, treosulfan, vinblastine, Marqibo® and BOLD regimen (bleomycin, vincristine, lomustine and dacarbazine).
Immunotherapy (n=13)	• Tebentafusp, bevacizumab, cixutumumab, glembatumumab, ipilimumab, nivolumab, pembrolizumab, tremelimumab, entinostat, tumour-infiltrating lymphocytes (TIL) and human leukocyte interferon.
Targeted therapy (n=13)	• Cabozantinib, everolimus ganetespib, imatinib, pasireotide selumetinib, sunitinib, sorafenib, trametinib and aflibercept.
Combination therapy (n=7)	• Dacarbazine+selumetinib, paclitaxel+selumetinib, carboplatin+paclitaxel+sorafenib, fotemustine+interferon α2 and IL-2,TIL+ cyclophosphamide, bevacizumab+temozolomide, BOLD regimen+human leukocyte interferon.

Liver directed therapies (LDTs): Chemotherapy with isolated hepatic perfusion (IHP)/percutaneous hepatic perfusion (PHP) (n=6); Trans-arterial chemoembolisation (TACE) (n=4); immunoembolisation (n=1) and yttrium-90 radioembolisation (n=2)

Results – Outcomes

- Results for median OS and PFS are presented in table 3.
- ORR ranged from 0 to 5% for chemotherapy; 0 to 34% for immunotherapy; 0 to 59% for targeted therapy; 0 to 35% for combination therapy and 16.7% to 100% for LDTs.
- DCR was reported in 51 studies and no specific trend was observed.
- 18 studies reported data on serious AEs and 26 on treatment related AEs. Most common adverse events reported were haematological, gastrointestinal, metabolic and skin-related.
- Seven studies used a variety of tools (like EORTC-QLQ-C30 , FACT-G/M) to report patient HRQoL .

Table 3: Key clinical trial results for metastatic UM

Median overall survival, systemic therapies	
RCTs (n=7)	• 6.35 to 21.7 months (based on 6 studies).
Single arm trials (n=33)	• Chemotherapy (n=11): 4.3 (dacarbazine and treosulfan) to 18 months (cisplatin, dacarbazine and vinblastine). • Immunotherapy (n=11): 3.1 (for pembrolizumab) to 29.6 months (for tebentafusp). • Targeted therapy (n=7): 4.9 (for ganetespib) to 19 months (aflibercept). • Combination therapy (n=4): 10 to 19.4 months (for immuno-chemotherapy).
Median overall survival, liver directed therapies	
RCTs (n=2) and single arm trials (n=10)	• Slightly higher for IHP vs IV fotemustine (14.6 vs 13.8 months). • For chemoembolization: a the range of 2.1 to 21.9 months. • Higher for immunoembolisation vs bland embolisation (21.5 vs 17.2 months). • For Yttrium-90 radioembolization: in the range 10 to 19.2 months.
Median progression free survival, systemic therapies	
RCTs (n=9)	• 1.8 to 5.5 months (based on 9 studies).
Single arm trials (n=29)	• Chemotherapy (n=9): 1.5 (for paclitaxel) to 7.6 months (for docetaxel plus carboplatin). • Immunotherapy (n=11): 2.1 (for pembrolizumab plus entinostat) to 11 months (pembrolizumab monotherapy). • Targeted therapy (n=6): 1.6 (for ganetespib) to 5.7 months (for aflibercept). • Combination therapy (n=3): 4.0 to 4.4 months (for immuno-chemotherapy and targeted-chemotherapy)
Median progression free survival, liver directed therapies	
RCTs (n=2) and single arm trials (n=8)	• IHP vs IV fotemustine: 4.5 vs 3.7 months. • Chemoembolization: 6.7 to 8.1 months. • IHP/PHP with melphalan: 6.6 to 9.0 months. • Immunoembolisation vs bland embolisation: 3.9 vs 5.9 months. • Yttrium-90 radioembolization: 3 to 8.1 months.

Discussion

- Studies presented clinical outcomes for systemic and localised LDT treatments.
- It was difficult to draw any meaningful comparisons across the studies
- Overall, the range of the median OS and PFS values were similar between immunotherapies, targeted therapies, and chemotherapies.
- Most recent clinical trials have tested immunotherapy treatments for metastatic UM. Of these, overall survival with tebentafusp was found to be greater compared to other immunotherapies.
- Only one published RCT demonstrated a systemic treatment with significant survival benefit. The results from this trial showed that patients treated with tebentafusp had an OS (21.7 vs 16 months) and PFS (3.3 vs 2.9 months) that was longer than the comparator arm (either dacarbazine ipilimumab or pembrolizumab) (7).
- Localised LDTs generally reported improved OS compared to systemic therapies, however only a minority of patients with metastatic UM are clinically eligible for localised LDTs.

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