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Insights of Clinical Case Reports

A 20-Year Real-World Benchmark of Metastatic Uveal Melanoma Outcomes in a Tebentafusp-Inaccessible Low- and Middle-Income Country (LMIC)

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1. Abstract

Uveal melanoma (UM) is a rare malignancy arising from melanocytes of the uveal tract. Despite effective local control, 10-50% of patients develop metastatic disease, which is associated with poor prognosis and a median overall survival (OS) of approximately one year. Real-world data especially from LMICs remain lacking. This study evaluates the clinical characteristics, treatment patterns, and survival outcomes of patients with metastatic UM treated in a LMIC.

1.2. Methods

This retrospective study included adult patients with metastatic UM treated and followed at King Hussein Cancer Centre in Amman, Jordan between 2006 and 2025. Collected data included baseline demographic and clinical characteristics as well as treatment patterns. Descriptive and survival analyses were conducted using JASP software (version 0.95.4). A two-sided P value <0.05 was considered statistically significant.

1.3. Results

Among 125 patients with UM, 31 (24.8%) had metastatic disease, including two patients with metastasis at initial presentation. Median age at diagnosis was 51 years, and 61.3% were males. ECOG performance status was 0–1 in 61.2% of patients. Hepatic-only metastases occurred in 51.6% of patients, combined hepatic and extrahepatic in 38.7%, and extrahepatic-only in 9.7%, with 54.8% classified as M1a disease. Median time to distant metastasis was 25 months. Median OS from initial UM diagnosis was 35 months, while median post-metastatic OS (PM-OS) was 10 months. First-line Immunotherapy was associated with significantly improved PM-OS compared to Dacarbazine (median 11 vs 5 months; P = 0.034), with 24-month PM-OS of 44.4% vs 0% respectively. Treatments included Immunotherapy, chemotherapy, targeted therapy in one patient, metastasis-directed local interventions, and best supportive care.

1.4. Conclusion

Metastatic UM remains associated with poor survival outcomes in this real-world cohort. First-line Immunotherapy was associated with longer survival compared to chemotherapy.

2. Introduction

Uveal melanoma (UM) is a rare malignancy that arises from melanocytes of the uveal tract, including the iris (3-5%), ciliary body (5-8%), and choroid (90%) [1].

[2]. Although it is a rare disease with an incidence of 5-6 per million in the USA, it accounts for 85% of primary ocular malignancies [3]. Despite their common origin from melanocytes, uveal and cutaneous melanomas differ in their genetic profile and clinical behaviour. Mutations in GNAQ and GNA11 appear to be the major contributors to the development of UM. In contrast, mutant BRAF, mutant RAS, and mutant NF1 are the most prevalent significantly mutated genes in cutaneous melanoma [4,5]. Moreover, UM is characterized by a relatively low tumour mutational burden (TMB) [6].

Local uveal melanoma can be treated with enucleation, globe-preserving surgeries, radiotherapy, or laser therapy. The majority of cases are treated with Iodine-125 brachytherapy, with no significant mortality differences among the use of different treatment options [7]. However, up to 50% of UM patients develop metastatic disease despite effective local control, mainly involving the liver, lung, and bone. The one-year overall survival rate for meta-

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static disease ranges from 13% to 40%, with a median survival of 6-12 months [8-10].

Management strategies primarily focused on liver-directed approaches for hepatic metastases, including surgical resection, Hepatic Intra-arterial Chemotherapy (HIAC), Trans arterial Chemoembolization (TACE), and Selective Internal Radiation Therapy (SIRT); however, none of these modalities has demonstrated a clear survival benefit to date [11]. In addition, conventional cytotoxic chemotherapy agents such as Dacarbazine, Temozolomide, and Cisplatin have shown limited clinical effects with response rates ranging from only 0% to 15% [12].

Several Immune Checkpoint Inhibitors have been approved for the treatment of metastatic cutaneous melanoma, including anti–CTLA-4 monoclonal antibodies and programmed death-1 (PD-1) inhibitors. Reported objective response rates range from 10.9% to 15.2% with anti–CTLA-4 agents and from 19% to 52% with anti-PD-1 therapies, with one-year overall survival rates approaching 74.1% in patients treated with PD-1 inhibitors [13-15]. In contrast, no large randomized clinical trials evaluating checkpoint inhibitor efficacy have been completed in metastatic UM, and the available evidence is derived primarily from small prospective cohorts and retrospective analyses [16].

More recently, Tebentafusp, a bispecific T-cell engager, emerged as the first-in- class agent to demonstrate a significant overall survival benefit in metastatic UM in a phase III randomized trial. However, its clinical activity is restricted to patients expressing HLA-A*02:01, thereby limiting its applicability to this subset of the population [17, 18].

Real-world evidence, particularly from low- and middle-income countries (LMICs), remains limited. This study aims to characterize the clinical features, treatment patterns, and survival outcomes of patients with metastatic UM managed in an LMIC setting.

Materials and Methods

2.1. Study Design

This is a single-centre retrospective study that was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was reviewed and approved by the Institutional Review Board of King Hussein Cancer Centre, Amman, Jordan. Study identification number is 25KHCC283, approval date: December 1, 2025. Individual consent for this retrospective analysis was waived and all data were anonymized to ensure confidentiality.

2.2. Participants

Adult patients with pathologically confirmed metastatic uveal melanoma who were treated and followed at King Hussein Cancer Centre (KHCC) between January 2006 and December 2025 were included in this study. The decision to administer systemic therapy was based on treating physician's assessment of patient comorbidities and performance status, anticipated systemic therapy tolerability, and shared decision-making with the patient. Patients with missing data on systemic therapy or those lost to follow-up were excluded.

2.3. Data Collection

Data was collected from KHCC medical records by the coauthors, and it included various patients' characteristics such as age at diagnosis, gender, ECOG performance score, largest metastatic lesion size, locations of metastasis, first-line systemic treatments, subsequent-line systemic treatments, and if any additional local interventions administered during metastatic-disease management. The collected data was verified by the first/corresponding author; at least 20% of the collected data was cross- checked by this author to ensure accuracy and reliability.

2.4. Statistical Analysis

A descriptive analysis was performed to summarize the various patient's characteristics including age at diagnosis, gender, ECOG performance score, largest metastatic lesion size, locations of metastasis, first-line systemic treatments, subsequent-line systemic treatments, and the additional metastasis-directed local interventions.

Time to metastasis is defined as interval between the initial diagnosis of uveal melanoma disease and the subsequent detection of metastatic disease. Overall survival (OS) is defined as the time from the initial diagnosis of UM to any-cause mortality as assessed by RECIST v1.1 criteria [19]. Post-metastasis progression free survival (PM-PFS) is defined as the time from the date of radiologic detection of metastatic UM to radiologic disease progression, as assessed by RECIST v1.1 criteria, or death from any cause, whichever occurs first. Post-metastasis overall survival (PM-OS) is defined as the time from the date of radiologic detection of metastatic uveal melanoma, as assessed by RECIST v1.1 criteria, to death from any cause.

Survival outcomes were estimated using the Kaplan–Meier method, and survival comparisons were conducted using the Log rank test and Cox proportional hazards regression. A two-sided P-value of <0.05 was considered statistically significant. All statistical analyses were performed in JASP software (version 0.95.4).

3. Results

3.1. Baseline Characteristics

A total of 215 patients with uveal melanoma were treated at KHCC. Among them, 86 patients with localized disease and 4 patients with metastatic disease were lost to follow-up. Consequently, 125 patients with uveal melanoma were treated and followed at KHCC, of whom 31 patients (24.8%) with metastatic disease were included in the present study, including two patients who had metastatic disease at initial presentation (Figure 1).

The median age at diagnosis was 51 years (range, 21-92, and 61.3% were males. An ECOG performance status of 0–1 was observed in 61.2% of patients, whereas 25.8% had a performance status of 2–4. Hepatic-only metastases were present in 51.6% of patients, combined hepatic and extrahepatic metastases in 38.7%, and extrahepatic-only metastases in 9.7%. According to metastatic staging, 54.8% of patients were classified as M1a, 29.0% as M1b, and 10.3% as M1c disease.

First-line treatments included Pembrolizumab in 15 patients (48.4%), Nivolumab plus Ipilimumab in 4 patients (12.9%), Dacarbazine chemotherapy in 3 patients (9.7%), Darovasertib plus Crizotinib in 1 patient (3.2%), and best supportive care alone in 8 patients (25.8%). Only 25.7% of patients received second-line therapies that consisted of Dacarbazine chemotherapy in 7 patients and Nivolumab plus Ipilimumab in 1 patient. Moreover, only 6.4% of all patients could reach to third-line therapies which included Carboplatin plus Paclitaxel chemotherapy in 1 patient and Single- agent paclitaxel in 1 patient.

Additional metastasis-directed local interventions were administered to selected patients and included radiotherapy in 9 patients (29.0%), microwave ablation in 1 patient (3.2%), and surgical resection in 1 patient (3.2%). Among those receiving radiotherapy, treatment sites included the spine (n= 4), liver (n= 3), and brain (n= 2). Baseline characteristic is illustrated in (Table 1).

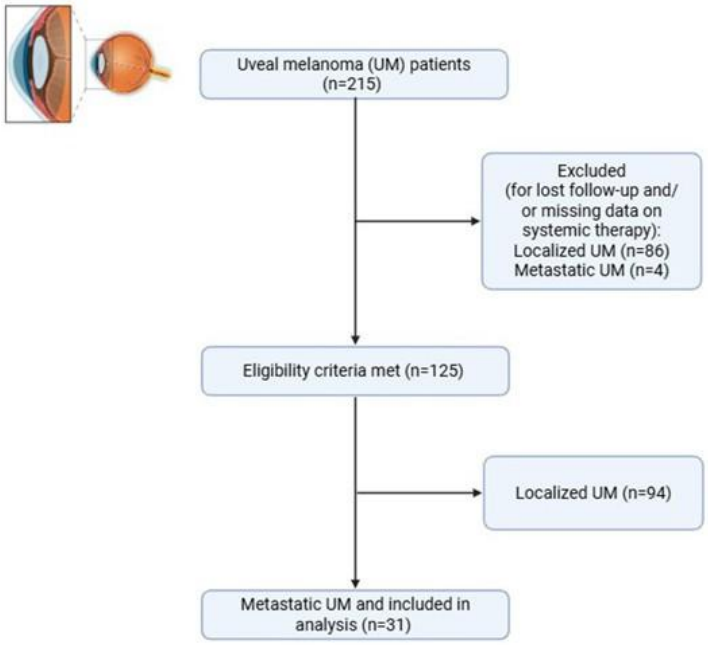

Figure 1: Study Cohort Flow Diagram.

Table 1: Baseline patients' characteristics (N=31).

Variable	Value	(%)Total n
Median age	years (range, 21- 51 .(92	
Sex	Male	(61.3%) 19
	Female	(38.7%) 12
Smoking history	Yes	(38.7%) 12
	No	(51.6%) 16
	missing	(9.7%) 3
ECOG performance score	0-1	(61.2%) 19
	02-Apr	(25.8%) 8
	missing	(13%) 4
Sites of metastasis	Hepatic-only	(51.6%) 16
	Combined Hepatic and Exrahepatic	(38.7%) 12
	Extrahepatic-only	(9.7%) 3
Stage of metastasis	M1a	(54.8%) 17
	M1b	(29.0%) 9
	M1c	(9.7%) 3
	missing	(6.5%) 2
First-line treatments	Pembrolizumab	(48.4%) 15
	Nivolumab plus Ipilimumab	(12.9%) 4
	Dacarbazine chemotherapy	(9.7%) 3
	Darovasertib plus Crizotinib	(3.2%) 1
	Best supportive care alone	(25.8%) 8
Second-line treatments	Dacarbazine chemotherapy	(22.5%) 7
	Nivolumab plus Ipilimumab	(3.2%) 1
Third-line treatments	Carboplatin plus Paclitaxel	(3.2%) 1

	Single-agent paclitaxel	(3.2%) 1
Additional metastasis- directed local interventions	Radiotherapy	(29.0%) 9
	Microwave ablation	(3.2%) 1
	Surgical resection	(3.2%) 1

3.2. Response to First-Line Treatments

The only patient who received first-line Darovasertib plus Crizotinib experienced disease progression (DP) on the first post-treatment CT evaluation.

Among the 3 patients treated with first-line Dacarbazine, 1 had DP, 1 discontinued therapy after the first cycle due to poor tolerance and transitioned to best supportive care, and 1 achieved a partial response.

Among the 19 patients who received first-line Immunotherapy, 2 achieved a partial response, 1 had a stable disease, 1 received two cycles and died before a formal response assessment could be performed, and 1 discontinued after a single cycle due to intolerance and transitioned to best supportive care. 14 patients exhibited radiological DP; however, 9 of these patients had no clinical deterioration and were therefore considered to have pseudo progression, with immunotherapy subsequently continued.

3.3. Survival Outcomes

At a median follow-up of 87 months, the median time to distant metastasis was 25 months. In the overall cohort, the median OS from initial UM diagnosis was 35 months, while median post-metastatic OS (PM-OS) was 10 months.

In univariable analyses, age was not associated with PM-OS (HR 1.001, 95%CI 0.975–1.028; P= 0.950), nor were sex (HR 0.92, 95%CI 0.399–2.145; P= 0.855), smoking history (HR 1.033, 95%CI 0.424–2.514; P= 0.944), metastatic stage (HR 1.939, 95%CI 0.536–7.013; P= 0.342), or location of metastasis (HR 1.139, 95%CI 0.251–5.171; P= 0.984). In contrast, ECOG performance score was significantly associated with PM- OS (HR 0.643, 95%CI 0.453–0.911; P= 0.009).

First-line Immunotherapy was associated with a statistically significant improvement in PM-OS, with a median survival of 11 vs. 5 months in the Dacarbazine cohort (HR 0.24, 95%CI 0.061–0.991; P= 0.034). Consistently, the 24-month PM-OS rate was 44.4% in the Immunotherapy group compared to 0% in the Dacarbazine group (Figure 2). However, in the multivariable Cox proportional hazards model adjusting for ECOG performance score, first-line Immunotherapy was not independently associated with improved PM-OS compared to Dacarbazine (HR 3.82, 95% CI 0.265–55.243).

Notably, the patients who continued first-line Immunotherapy despite radiological DP, consistent with pseudo progression, demonstrated significantly improved PM-OS by log-rank analysis compared with those who discontinued Immunotherapy upon radiological DP (median 32 vs. 6 months; p = 0.020). Despite this, the association was not maintained in the Cox proportional hazards model (HR 0.27, 95% CI 0.067–1.101) (Figure 3).

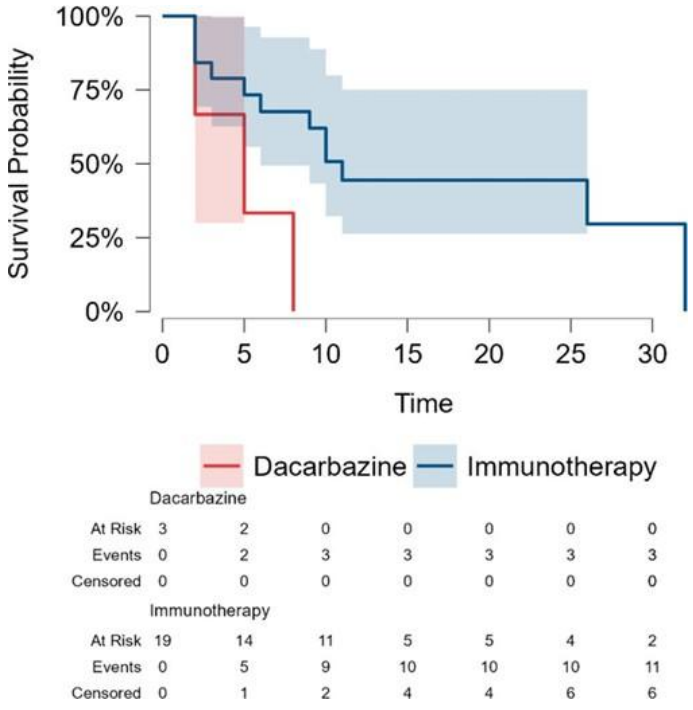

Figure 2: First-line treatments PM-OS.

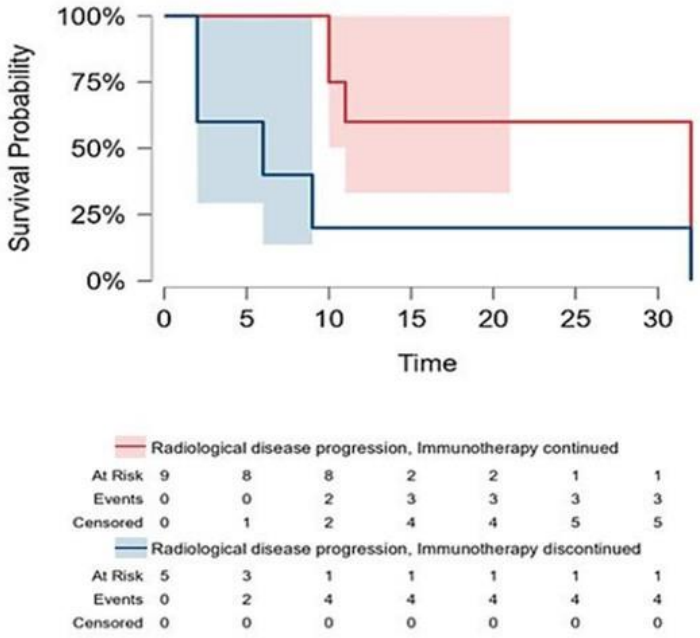

Figure 3: PM-OS for first-line Immunotherapy following radiological disease progression.

4. Discussion

In this real-world cohort of patients with metastatic UM, median OS was 35 months, while median PM-OS was 10 months, underscoring the aggressive clinical course of the disease and aligning with previously published historical data [8,9,20]. First-line Immunotherapy was associated with a longer median PM- OS compared with Dacarbazine (11 vs. 5 months; P = 0.034), with a 24-month PM-OS rate of 44.4% versus 0%, respectively. These findings are consistent with contemporary prospective trials and real-world series, including the GEM- 1402 phase II study, which reported a median OS of 12.7 months with first-line Nivolumab plus Ipilimumab 16. Similarly, a large Japanese meta-analysis including 41 cohorts and 1,414 patients with metastatic uveal melanoma treated with Immunotherapy reported a pooled median OS of 11.2 months 21. Taken together, these data support an association between Immunotherapy and prolonged survival in a subset of patients. Importantly, our findings offer real-world insight for centres where newer agents, such as tebentafusp, remain inaccessible and reflect the evolving therapeutic landscape of metastatic UM. Baseline ECOG performance status emerged as a strong independent prognostic factor for survival in our cohort. Although first-line Immunotherapy was associated with longer PM-OS compared with Dacarbazine, this association was not maintained after adjustment for ECOG performance status, suggesting that functional status substantially influenced observed outcomes. This likely reflects confounding by indication, whereby patients with better baseline functional status were preferentially selected for Immunotherapy. This is consistent with prior metastatic UM cohorts demonstrating that performance status at the time of metastatic diagnosis independently predicts survival [22]. Together, these findings highlight the importance of patient selection in real-world treatment patterns and underscore the need for prospective studies to better define the independent survival impact of Immunotherapy in this population.

A notable and novel observation in our cohort was the apparent survival advantage among patients who continued first-line Immunotherapy despite radiologic progression consistent with pseudo progression. Patients who remained on immunotherapy demonstrated longer PM-OS compared with those who discontinued treatment at the time of radiologic disease progression (median 32 vs. 6 months; P = 0.020). With Immunotherapy, a subset of patients may demonstrate radiologic enlargement of existing lesions or the appearance of new lesions that do not reflect true tumor progression, a phenomenon referred to as pseudo progression. While pseudo progression is well described in cutaneous melanoma, reports in UM remain limited, with only isolated case reports published to date, including a patient treated with Nivolumab in 2017, and another treated with Pembrolizumab in 2023 [23,24]. Our findings provide additional real-world evidence suggesting that pseudo progression can occur in UM. One of the limitations of these findings, that this association was not maintained in cox proportional hazards modelling, likely reflecting limited sample size, potential violation of proportional hazards assumptions, and the phenomenon of immortal time bias, whereby patients who survived long enough to be observed continuing therapy necessarily had longer survival. Lead time bias may also have contributed, as patients selected to continue therapy were clinically stable and able to undergo repeat imaging. As a result, some of the apparent benefits may reflect selection of patients with inherently more indolent disease biology rather than a true treatment effect. Although hypothesis generating, our results suggest that in carefully selected, clinically stable patients, continuation of Immunotherapy beyond initial radiologic progression may warrant consideration, while emphasizing the need for prospective validation.

Accurate identification of pseudo progression remains challenging when conventional RECIST criteria are applied to patients treated with Immunotherapy. Immune-adapted response frame-

works, such as iRECIST, have been proposed to better distinguish atypical immune-related responses from true disease progression. In advanced melanoma, a retrospective cohort study suggested that lowering the iRECIST progression threshold and incorporating early sequential restaging scans may improve detection of pseudo progression and are associated with more favourable survival outcomes [25]. Although these data are derived from cutaneous melanoma, they highlight the limitations of standard response criteria in the Immunotherapy era and support further evaluation of immune-modified imaging approaches in UM to better characterize delayed treatment effects and refine prognostic stratification.

Overall, these study findings should be interpreted in the context of a retrospective, single-centre design with a limited sample size and the potential for residual confounding.

Nonetheless, this study provides a pragmatic benchmark for outcomes in resource-constrained settings and highlights ongoing unmet needs in metastatic UM. Our results also underscore disparities in access to emerging therapies, such as tebentafusp, in LMICs, emphasizing the importance of expanding access to novel agents and broadening inclusion of patients from these regions in future clinical trials.

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