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CASE REPORT

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Advances in the therapeutic management of metastatic uveal melanoma including real-world experience with tebentafusp

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ABSTRACT

Uveal melanoma is the most common malignant neoplasm of the eyeball. It develops from melanocytes of the uveal membrane of the eye, and it significantly differs from melanoma in terms of clinical behavior and therapy compared to other localizations. The survival of patients in metastatic settings is still poor and poses significant challenges.The most important factor determining the length of survival of these patients is the presence of metastases in the liver, which is the most common site of metastasis (70–90% of cases) and the only site in about 50% of cases. Survival from the point of finding metastatic lesions in the liver is usually short, with a median of a few months. In a systematic review of approximately 800 patients, overall survival (OS) in the group treated with systemic chemotherapy was 9 to 15 months compared to operated patients with survival of 10 to 35 months. For many years, studies testing systemic therapies have not yielded any positive results . The only exception is tebentafusp (IMCgp100), which is a new bispecific molecule targeting T cells in the presence of HLA-A*02:01. Currently, it is the only drug approved for systemic therapy of metastatic uveal melanoma with confirmed improvement in OS. In the present issue of *Oncology of Clinical Practice*, we present an international series of interesting case reports on using tebentafusp in clinical practice outside of clinical trials in patients with metastatic uveal melanoma.

Keywords: metastatic uveal melanoma, tebentafusp, systemic treatment

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Introduction

Uveal melanoma is the most common malignant neoplasm of the eyeball in adults, which develops from melanocytes of the uveal membrane of the eye and differs substantially from skin and mucosal melanomas. The distribution of uveal melanoma differs by sex, ethnicity, and geography from that of cutaneous melanoma. Every year, 5 to 10 new cases of uveal melanoma are diagnosed per 1 million people worldwide. The incidence of uveal melanoma varies depending on ethnicity and latitude and is most common in Caucasians (98% of all patients) and at higher latitudes [1–6]. This cancer is rare in children and has a better prognosis [7, 8]. Risk factors for uveal melanoma also include fair skin, light eye color, and a tendency to get sunburn. Moreover, a higher incidence of this illness was observed in welders [9–13]. The relationship between

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the occurrence of ocular melanoma and skin melanoma has been confirmed in a few clinical studies, while other analyses have not confirmed such a relationship [14–17].

In most cases, at the time of diagnosis, the disease is limited to the eye, and only about 3% of patients are diagnosed in the metastatic stage. A significant number of patients develop distant metastases within 20 years after treatment of primary uveal melanoma, depending on the disease stage at the diagnosis of the primary tumor (20% in patients in stage I, 70% in stage III) and the genetic abberations [18, 19]. Larger tumors are associated with worse prognosis, and an increase in tumor height by 1 mm increases the risk of metastasis within 10 years by 5% [20, 21]. More than 30% of patients with melanoma involving the ciliary body, 25% with choroidal tumors, and 7% with iris tumors develop distant metastases within 10 years of diagnosis. In up to 90% of cases, metastases are located in the liver, and the liver is the only site of metastasis in about 50% of patients. Metastases may also develop in other locations, including the lungs, bones, skin, and soft tissues, but they are very rare in lymph nodes [22]. The prognosis in those with liver metastases is poor, and treatment can prolong survival by several months, depending on the possibility of using local and systemic treatment methods. The median survival time is approximately 2–3 months. Based on a systematic review of approximately 800 patients, overall survival (OS) in the group treated with systemic chemotherapy ranged from 9 to 15 months compared to 10–35 months in patients after surgery [1, 2, 23–25]. Complete resection of liver metastases should be considered whenever possible. Usually, resection of two liver segments is performed. The procedure is most often used in patients with expected long survival, in whom potentially radical resections (R0) are possible and there are no lesions located outside the liver. Methods of local treatment include resection, isolated liver perfusion, intra-arterial chemoinfusion, transarterial chemoembolization, immunoembolization, selective radiotherapy, and thermal ablation methods [radiofrequency ablation (RFA), microwave ablation (MWA)]. In some cases, laparoscopic surgery is an option [1, 2].

Systemic treatment options in metastatic disease are limited. Studies with systemic therapies have not yielded any positive results, and the efficacy of classic chemotherapy is small [3]. Data from a meta-analysis that included 965 patients with metastatic uveal from 29 prospective studies have shown median progression-free survival (PFS) of 3.3 months and median OS of 10.2 months. The analysis was done based on systemic therapy used for metastatic uveal melanoma treatment. The median PFS and OS rates were significantly longer in patients treated with liver-directed therapy. Median PFS for each treatment group was 2.8 months in patients treated with immunotherapy, 2.8 months for kinase inhibitors, 2.8 months for anti-angiogenic drugs, 2.6 months for chemotherapy, and 5.2 months for liver-directed therapy. The median OS rate for each treatment group was 8.9 months for immunotherapy, 9.1 months for kinase inhibitors, 11.0 months for anti-angiogenic drugs, 9.2 months for chemotherapy, and 14.6 months for liver-directed therapy. Based on univariable analysis, shorter PFS was associated with elevated lactate dehydrogenase (LDH), elevated alkaline phosphatase (ALP), and liver metastases above 3 cm [26]. Some chemotherapy regimens have been tested in prospective trials in patients with metastatic uveal melanoma. Based on these studies, it is unclear if monotherapy regimens improve survival [24]. Based on four prospective clinical trials with combined chemotherapy regimens, median PFS was from 2.5 to 6.7 months, and median OS from 7.5 to 14.2 months [27–30]. A commonly used combined chemotherapy includes cisplatin, vinblastine, and dacarbazine (CVD regimen) with median OS of 9.0 months [31]. There are data from clinical trials supporting the efficacy of the dacarbazine, vincristine, bleomycin, and lomustine (BOLD regimen) combined with interferon [32]. The efficacy of immune checkpoint inhibitors is also limited; some small effects were observed using the combination of nivolumab and ipilimumab. However, meta-analyses have shown that the treatment results are not superior to conventional chemotherapy [33–36].

A drug that showed some effectiveness in the treatment of uveal melanoma was tebentafusp (IMCgp100), which is a bispecific fusion protein comprised of a T cell receptor (TCR; targeting domain) fused to an antibody fragment targeting CD3 (cluster of differentiation 3; effector domain). The TCR end binds with high affinity to a gp100 peptide presented by human leukocyte antigen — A*02:01 (HLA-A*02:01) on the cell surface of uveal melanoma tumor cells, and the effector domain binds to the CD3 receptor on the polyclonal T cell [37]. Tebentafusp is currently the only drug approved for systemic therapy of metastatic uveal melanoma with confirmed OS improvement. This drug was assessed in a large, randomized, phase III trial in 378 previously untreated HLA-A*02:01 positive metastatic uveal melanoma patients. Patients were randomized in a 2:1 ratio to receive tebentafusp or a drug of the investigator's choice (pembrolizumab, ipilimumab, or dacarbazine monotherapy). The OS rate at 1 year was significantly higher in the tebentafusp group compared to the control group [73% *vs.* 59%; hazard ratio (HR) = 0.51; 95% confidence interval (CI) 0.37–0.71; $p < 0.001$], the PFS rate was also higher (31% *vs.* 19%; HR = 0.73; 95% CI 0.58–0.94; $p = 0.01$) [37]. Median OS after 36 months of follow-up (median) was 21.6 months in the tebentafusp group and 16.9 months in the control group (HR = 0.68; 95% CI 0.54–0.87). The most common treatment-related

adverse events of any grade in the tebentafusp group were rash (83%), pyrexia (76%), pruritus (70%), and hypotension (38%). The adverse events were mostly observed at the beginning of treatment, and usually, no new adverse events related to tebentafusp were reported during long-term follow-up. No treatment-related deaths were reported, but only 2% of patients in the tebentafusp group completed treatment due to toxicity, compared to 5% in the control group. Improved OS was also observed in the group treated after disease progression; therefore, continuation of tebentafusp treatment after disease progression may be considered if the treatment is well tolerated [38–40]. The drug was approved for use in the European Union in 2022. It may induce side effects, including cytokine release syndrome, so the patients have to be observed in the hospital for 24 hours after administration of each of the first three doses [37].

In the Department of Soft Tissue/Bone Sarcoma and Melanoma Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw, Poland, more than 550 patients with uveal melanoma have been followed and treated with different modalities. One hundred thirty-two patients have been treated with chemotherapy alone, few patients received immunotherapy or targeted therapy, and around 50 received tebentafusp in clinical trials and expanded-access programs in different treatment lines, with or without chemotherapy in other treatment lines. Sixty-seven patients received 1 line of systemic chemotherapy, 33 patients 2 lines, 20 patients 3 lines, 11 patients 4 lines, and 1 patient 6. The mean number of chemotherapy regimens was 2. In the first line, the most frequently used regimen was CVD (63 patients) and BOLD (47 patients); other regimens included paclitaxel, fotemustine, lomustine, platinum compounds, dacarbazine, vinblastine, vincristine, cyclophosphamide in monotherapy or different combinations. In the second line, the most commonly used regimens were paclitaxel in monotherapy (29 patients) or in combination with platinum compounds (5 patients), CVD (13 patients), and BOLD (8 patients). The most commonly used regimens in the third line were BOLD (10 patients) and paclitaxel in monotherapy (9 patients) or in combination with platinum compounds (6 patients). Median OS in patients treated with chemotherapy alone was 9.0 (7.2–11.4) months [n = 98, OS analysis done for patients treated with dacarbazine (DTIC) or regimens containing dacarbazine in first line and chemotherapy alone] (Fig. 1). Forty-two patients have been treated with tebentafusp in the expanded-access program, with median PFS of 5.6 months (4.1–6.2) and median OS of 13.4 months (10.5–not reached). About 50% of patients have continued treatment beyond progression. The safety profile was consistent with what is known from clinical trials.

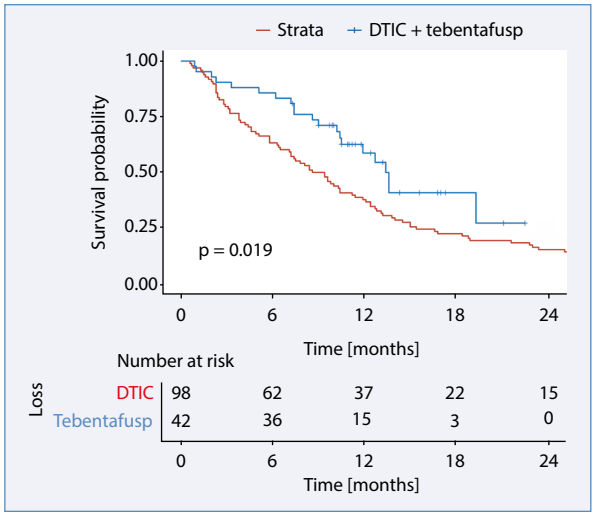

Figure 1. Overall survival (OS) in patients treated with dacarbazine (DTIC) or regimens containing DTIC in first line and chemotherapy alone and patients treated with tebentafusp

Case report 1

A case report of a female patient who was treated with tebentafusp for metastatic uveal melanoma of the right eye.

In April 2020, the patient experienced loss of vision in the right eye and vertigo. Due to these symptoms, the patient was consulted by an ophthalmologist. Ultrasound of the right eyeball revealed a choroidal tumor measuring 8.5 mm at its thickest point and 17 mm in diameter. Based on ophthalmological examinations, the patient was diagnosed with uveal melanoma. The stage was T3, according to the American Joint Committee on Cancer (AJCC) (Fig 2). At the time of diagnosis, the patient was 25 years old and did not suffer from any chronic diseases. In May 2020, the patient underwent brachytherapy with Iodine-125. The therapy was complicated by radiation retinopathy. For this reason, the patient received anti-VEGF injections into the right eye. Follow-up examinations in October 2020 showed regression of the tumor.

On November 21, 2022, a follow-up ultrasound examination of the abdomen revealed suspicious hypoechoic lesions in the liver. The patient was then 29 weeks pregnant. Magnetic resonance imaging of the abdominal cavity without intravenous contrast showed polycyclic lesions in the 3rd segment of the liver, measuring 3.2 × 2 × 3 cm, and five smaller lesions in the right lobe, up to 1.7 cm (Fig 3). The lesions had radiological features of uveal melanoma metastasis to the liver. Due to the typical course of the disease, the characteristic appearance of nodular lesions in the liver, and ongoing pregnancy, it was decided not to perform a biopsy to

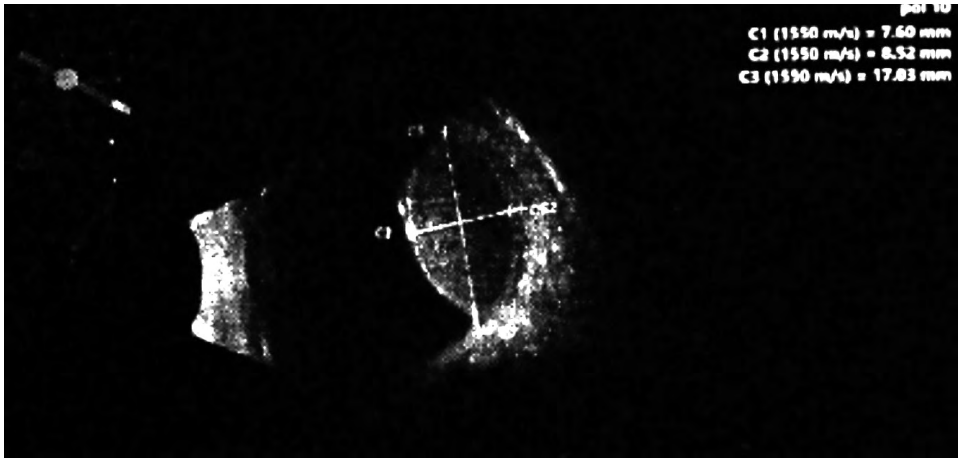

Figure 2. Ultrasound from May 2020 showed a right eye tumor

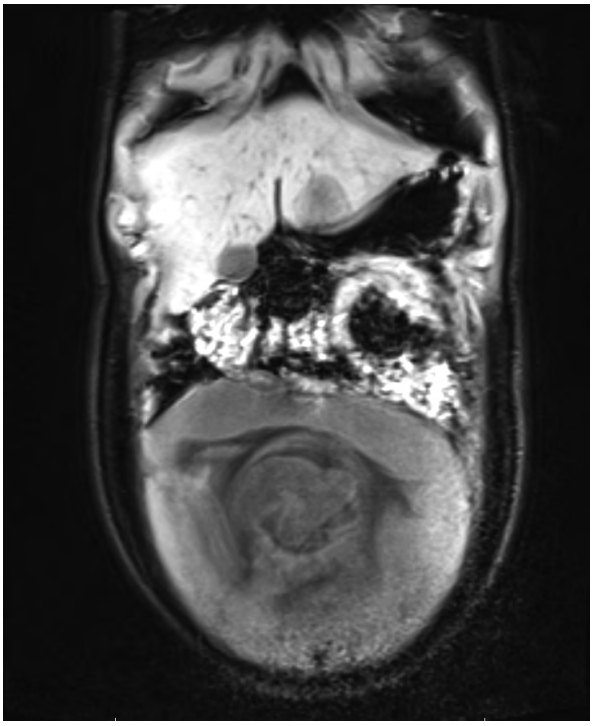

Figure 3. Abdomen magnetic resonance imagining (MRI) from 29.11.2022 showed a metastatic lesion to the right lobe of the liver.

confirm the spread of the disease pathologically. After a gynecological consultation and consultation with the patient, a decision was made to continue the pregnancy. On February 2, 2023, the patient underwent a cesarean section (it was the 36th week of pregnancy) and gave birth to a healthy daughter (weight 2400 g, Apgar 10). Abdominal magnetic resonance imagining (MRI) with intravenous contrast on February 16, 2023, showed enlargement of the metastatic lesions in the liver to dimensions of 4.6 × 2.8 × 4.5 cm in the 3rd liver segment and up to 1.9 cm in the 6th segment. Ten smaller metastatic lesions were also found.

The test result for the presence of the HLA A*02:01 allele in the patient's peripheral blood was positive. On February 20, 2023, tebentafusp treatment was started. The patient tolerated the initial treatment well: during the first three cycles, she developed a fever of grade 1 according to Common Terminology Criteria for Adverse Events (CTC AE) and a rash of grade 2 according to CTC AE. Both adverse events did not occur after the 4th cycle. The first follow-up magnetic resonance imaging examination of the abdominal cavity on May 24, 2023, showed a reduction in the size of metastatic lesions (Fig. 4). It was a stable disease, according to the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. A follow-up magnetic resonance imaging examination of the abdominal cavity on February 28, 2024, showed continued disease stabilization according to RECIST 1.1. Periodically performed computed tomography did not show any metastatic lesions outside the liver. The patient continued treatment with tebentafusp at a dose of 68 μg intravenously every seven days. The longest breaks between cycles were two weeks; they were related to days off and not to side effects. On June 10, 2024, the patient received the 65th cycle of tebentafusp.

Case report 2

A 58-year-old male was diagnosed with T4 choroidal melanoma in June 2016 and was initially treated with proton irradiation therapy in Switzerland. In May 2019, MRI of the abdomen showed liver metastases. A biopsy confirmed melanoma diagnosis, and he was referred to

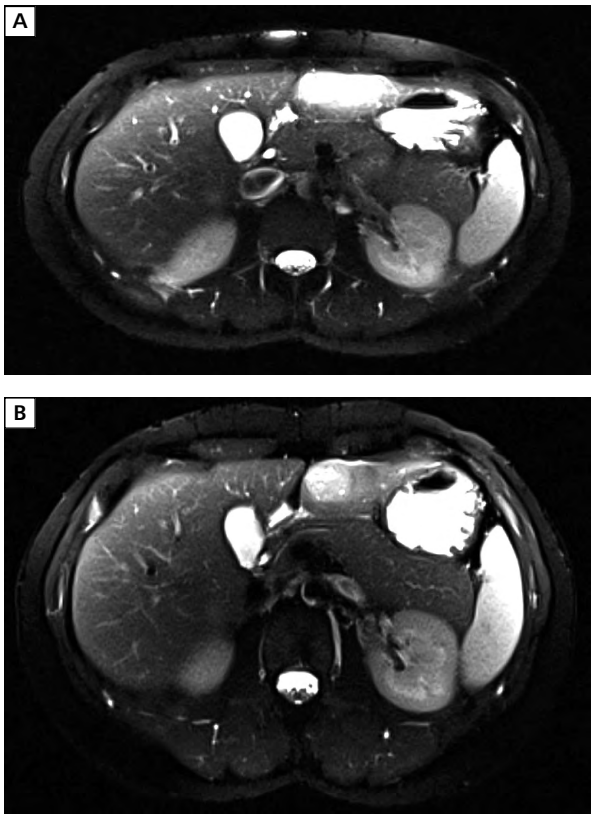

Figure 4. Abdomen magnetic resonance imagining (MRI) from February 16, 2023 (**A**) and May 24, 2023 (**B**). There is a visible reduction of the metastatic lesion in segment 3 of the liver

the National Cancer Institute (NCI) in Vilnius. A computed tomography (CT) scan of the chest and pelvis revealed no metastases. Genetic testing revealed a mutant *GNAQ*, which is frequently observed in uveal melanoma with stable microsatellite status and a low tumor mutational burden (TMB) of 1 Mut/Mb.

The case was discussed at the NCI cancer tumor board, and a decision was made to initiate treatment with stereotactic radiotherapy for liver metastases in the hope of achieving an abscopal effect, followed by ipilimumab and nivolumab. Stereotactic radiotherapy was administered to the two largest metastases (24 Gy in two fractions). However, the patient opted to continue treatment in Western Europe. In September 2019, in Germany, the patient enrolled in the IMCgp100-202 clinical trial (pembrolizumab arm) and received two cycles of pembrolizumab treatment. However, the treatment was discontinued at the patient's request despite good tolerability.

From October 2019 to January 2020, chemo saturation with melphalan was performed, and the patient completed three cycles but discontinued due to progressive thrombocytopenia. Subsequently, the patient underwent four cycles of treatment with ipilimumab and nivolumab, followed by nivolumab monotherapy in Bonn until March 2021.Top of Form

Due to disease progression in the liver, the patient returned to Zurich, where he was re-enrolled in the crossover arm of the IMCgp100-202 trial. He was treated weekly with tebentafusp, and during the first three infusions, he experienced grade 2 pyrexia and rash. Treatment with tebentafusp continued until August 2022, resulting in a partial response.

Because of the closure of the IMCgp100 trial, it was decided in the patient's best interest to continue treatment through an early access program at the National Cancer Institute in Vilnius. Treatment with tebentafusp was maintained. In April 2023, CT and MRI scans revealed disease progression in the liver. We chose to persist with tebentafusp and performed ablation procedures to address the increased liver metastases. The ablation procedures for liver metastases were carried out in May and August 2023. Regrettably, in August 2023, CT and MRI scans showed ongoing disease progression.

The patient was seen at the National Cancer Institute on September 1, 2023. His performance status remained at 1, liver function tests were within normal limits, and he expressed interest in exploring other treatment options, such as transarterial chemoembolization (TACE). In the middle of September, a TACE procedure with cisplatin was performed. Unfortunately, the patient's liver function gradually deteriorated, and in October, he was admitted for pyrexia and jaundice at Klaipeda University Hospital, where he passed away.

Case report 3

A 40-year-old male was referred to an ophthalmologist due to impaired vision of the left eye. He was diagnosed with melanoma of the uvea in December 2013. No distant metastases were present at the time of the diagnosis. The patient was hospitalized at the Clinic for Ophthalmology at University Hospital Centre Zagreb in January 2014, and the following procedures were performed: transpupillary thermotherapy (TTT) of the left eye, brachytherapy of the left eye (installation of the Ru 106 applicator in the left eye), and finally, on 8.02.2013, extraction of the Ru 106 CCB applicator from the left eye. Follow-up was recommended. In November 2016, liver metastases were detected with ultrasound. Positron emission tomography-computed tomography scan (PET-CT) confirmed oligometastatic, liver-only disease. The patient was then presented to the abdominal surgeon, and in December 2016, a liver metastasectomy was performed. The specimen underwent *BRAF* testing for mutations (the result was negative). After metastasectomy, regular follow-up was performed.

In March 2018, a routine CT scan detected multiple lung metastases. The CT-guided biopsy was carried out. Histopathology confirmed melanoma metastasis. Due to an inoperable disease, we applied dacarbazine--based chemotherapy from April until November 2018. During chemotherapy sessions, lung metastasis specimens underwent *BRAF* testing. A mutation was detected (double check performed). Since the result of *BRAF* testing was positive, the multidisciplinary team (MDT) for melanoma treatment approved dabrafenib and trametinib therapy in May 2019. A detailed physical examination and multiple endoscopies excluded new primary skin or mucosal melanoma. The patient was treated with BRAF and MEK inhibitors until December 2020, when progression in the liver occurred (new metastases). Therapy was discontinued, and due to limited progression in the liver, we decided to perform stereotactic body radiation therapy of liver metastases. Positron emission tomography-computed tomography scan in February 2021 showed a stable disease. Performance status was still Eastern Cooperative Oncology Group (ECOG) performance status 0, and the patient reported no symptoms.

Next, the MDT discussed options. Immunotherapy with ipilimumab-nivolumab was not reimbursed in Croatia for uveal melanoma so HLA testing was performed. The patient was HLA A0201 positive, and he was advised to apply for a donation program with tebentafusp in Germany. In September 2021, the patient received approval for treatment with tebentafusp in Munich, Germany. The patient started treatment after restaging procedures with PET-CT and brain MRI done in Munich, Germany and continued treatment in Zagreb, Croatia, at UHC Zagreb from September 2022 and continued therapy. The last follow-up was in February 2024. The patient's performance status continued to be excellent, without any significant toxicities. Multiple restaging procedures with PET-CT and brain MRI were done during his 2.5-year therapy with tebentafusp. Results were mostly stable disease (SD) according to RECIST criteria, with target lesions volume oscillations.

Case report 4

A 44-year-old female was referred to an ophthalmologist due to impaired vision of the right eye. She was diagnosed with malignant melanoma of the uvea (T3b N0 M0) in September 2018. No distant metastases were present at the time of the diagnosis. Her initial treatment was local brachytherapy with good results, and she was regularly followed up. During a routine follow-up, a local recurrence was diagnosed after 22 months, and repeated local brachytherapy was performed.

Advanced disease was diagnosed 4 years after the initial diagnosis and 4 months after the recurrence treatment in November 2020. The initial plan was to remove the liver lesion, but surgery was not feasible due to more extensive spread in the liver.

At the time of diagnosis of advanced disease, next-generation sequencing (NGS) testing Foundation Medicine One detected a GNAQ gene mutation.

In December 2020, the patient started conventional taxane-based chemotherapy but requested to stop it after the first cycle due to impairment of quality of life.

The patient started combination immunotherapy with ipilimumab 3 mg/kg with nivolumab 1 mg/kg every 3 weeks in a total of 4 cycles in May 2021. After cycle 4, hypophysitis was detected by MRI and lower adrenocorticotropic hormone (ACTH) and cortisol levels. Substitution therapy with hydrocortisone was started and nivolumab 240 mg every two weeks was continued. The first evaluation in September 2021 was a progressive disease according to RECIST criteria. In November 2021, it was concluded that the previous imaging had been pseudo-progression, as the largest lesion in the liver had decreased to 30%. In addition, the previously described extrahepatic lesions had also disappeared. Nivolumab maintenance therapy was continued until March 2022 without additional toxicity, but the disease was progressive.

The patient started tebentafusp therapy in June 2022. An HLA-02:01 positivity test was previously performed. At the beginning of the treatment, her performance status was good (ECOG 0). After the first two cycles with dose escalation, according to the product characteristics the patient continued on tebentafusp at 68 mcg per week. At the start of the treatment, skin rash (G2) was treated with topical therapy, and pyrexia (after 24 hours) was controlled with acetaminophen/paracetamol. The patient continued tebentafusp treatment until the disease had the best radiological response. In total, she received 78 cycles of tebentafusp without further adverse events. Her performance status continued to be excellent.

Discussion

Until 2022, there has been no dedicated and commonly recommended therapy for metastatic uveal melanoma. The clinical efficacy of multiple systemic therapies was evaluated in prospective clinical trials for the treatment of this disease, including immunotherapy, chemotherapy, targeted therapies, and a combination of systemic therapies. Several larger randomized phase II/III trials comparing systemic therapies in metastatic uveal melanoma did not show greater efficacy of new systemic therapies compared to chemotherapy, except

recent data for tebentafusp (dedicated to HLA-A*02:01-positive patients). All studies (except the study with tebentafusp) were non-control studies. Most often, the observations were retrospective and were carried out on small populations below 50 patients.

A comparison of median OS and PFS from the identified studies indicates a wide range of reported outcomes, with the median value for OS around 1 year and the median value for PFS around 3 months. However, due to the low reliability of the evidence, the results should be interpreted with caution. Many authors point out the disappointing results of reported outcomes and poor prognosis of patients with metastatic uveal melanoma. However, several drugs (including tebentafusp) targeting the new checkpoints showed optimistic results [38–41]. Looking at the results from early phase studies and the phase III study with tebentafusp, there is a significant difference in number of patients included. The study was randomized, and the study drug was compared with the standard of care based on the investigator's choice (pembrolizumab, dacarbazine, ipilimumab). This increases the reliability of the results from the phase III study with tebentafusp in HLA-A*02:01-positive patients with previously untreated metastatic uveal melanoma. The values for median OS were 21.6 months in the tebentafusp group and 16.9 months in the control group [38–40]. The median OS value in patients treated with tebentafusp in the Department of Soft Tissue/Bone Sarcoma and Melanoma in the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw, Poland, was 13.4 months. Median OS in patients treated with dacarbazine-based chemotherapy alone was 9.0 (7.2–11.4). Many patients were treated with tebentafusp in the second and subsequent lines of treatment, which may have impacted the OS results. We presented four cases of patients treated with tebentafusp in clinical practice, which confirm the efficacy and safety of this drug.

Conclusions

Metastatic uveal melanoma is a rare disease with a poor prognosis. The main location of metastases is the liver, and liver-directed therapy should be used whenever possible. The systemic treatment may be used if there is no option for local treatment, and there were limited options before tebentafusp approval. Tebentafusp (IMCgp100) is a new bispecific molecule targeting T cells in the presence of HLA-A*02:01 and is currently the only drug approved for systemic therapy of metastatic uveal melanoma. Based on phase III clinical trial results and data from clinical practice presented in this publication, tebentafusp prolongs OS and is more effective than chemotherapeutic agents. The safety profile is well known, and appropriate measures may be used to prevent and treat adverse events.

Article Information and Declarations

Data availability statement

The data that support the findings of this study are available from the authors, upon reasonable request.

Ethics statement

The article has been conducted according to the principles stated in the Declaration of Helsinki.

Author contributions

P.Rutkowski, M.D.-S.: methodology, conceptualization, investigation, writing — original draft, review, and editing; V.U., P.Rogala, L.S., K.P.: investigation, writing — original draft; P.T.: investigation, data analysis.

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Conflict of interest

P.Rutkowski: consulting fees: Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Philogen, Pfizer, Genesis, Medison Pharma; honoraria for lectures and writing: Bristol-Myers Squibb, MSD, Novartis, Pfizer, Pierre Fabre, Sanofi, Merck, Astra Zeneca; research funding: Novartis, Pfizer, Roche, Bristol-Myers Squibb.
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V.U., L.S., K.P., P.T.: declare no conflicts of interest.

Supplementary material

None.

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