World Journal of
Clinical Oncology

Contents

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Clinical Oncology*, Hui-Xia Lu, PhD, Professor, Department of Gynecology and Obstetrics, Clinical Medical College, University of Dali, Dali 671003, Yunnan Province, China. haohao021021@foxmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Oncology* (*WJCO*, *World J Clin Oncol*) is to provide scholars and readers from various fields of oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCO mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

INDEXING/ABSTRACTING

The *WJCO* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJCO* as 2.8; IF without journal self cites: 2.8; 5-year IF: 3.0; Journal Citation Indicator: 0.36.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xiang-Di Zhang*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Xu Guo*.

Uveal melanoma: Recent advances in immunotherapy

Francesco Saverio Sorrentino, Francesco De Rosa, Patrick Di Terlizzi, Giacomo Toneatto, Andrea Gabai, Lucia Finocchio, Carlo Salati, Leopoldo Spadea, Marco Zeppieri

Francesco Saverio Sorrentino, Patrick Di Terlizzi, Department of Surgical Sciences, Unit of Ophthalmology, Ospedale Maggiore, Bologna 40100, Italy

Francesco De Rosa, Department of Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori", Meldola 47014, Italy

Giacomo Toneatto, Andrea Gabai, Lucia Finocchio, Carlo Salati, Marco Zeppieri, Department of Ophthalmology, University Hospital of Udine, Udine 33100, Italy

Leopoldo Spadea, Eye Clinic, Policlinico Umberto I, "Sapienza" University of Rome, Rome 00142, Italy

Corresponding author: Marco Zeppieri, BSc, MD, PhD, Doctor, Department of Ophthalmology, University Hospital of Udine, p.le S. Maria della Misericordia 15, Udine 33100, Italy. markzeppieri@hotmail.com

Abstract

Uveal melanoma (UM) is the most common primary intraocular cancer in adults. The incidence in Europe and the United States is 6-7 per million population per year. Although most primary UMs can be successfully treated and locally controlled by irradiation therapy or local tumor resection, up to 50% of UM patients develop metastases that usually involve the liver and are fatal within 1 year. To date, chemotherapy and targeted treatments only obtain minimal responses in patients with metastatic UM, which is still characterized by poor prognosis. No standard therapeutic approaches for its prevention or treatment have been established. The application of immunotherapy agents, such as immune checkpoint inhibitors that are effective in cutaneous melanoma, has shown limited effects in the treatment of ocular disease. This is due to UM's distinct genetics, natural history, and complex interaction with the immune system. Unlike cutaneous melanomas characterized mainly by BRAF or NRAS mutations, UMs are usually triggered by a mutation in GNAQ or GNA11. As a result, more effective immunotherapeutic approaches, such as cancer vaccines, adoptive cell transfer, and other new molecules are currently being studied. In this review, we examine novel immunotherapeutic strategies in clinical and preclinical studies and highlight the latest insight in immunotherapy and the development of tailored treatment of UM.

Key Words: Uveal melanoma; Immunotherapy; Ocular oncology; Tumor; Metastatic disease; Genetic mutations

Core Tip: Our minireview will cover the latest studies about immunotherapy for uveal melanoma (UM) metastatic disease. Driver genes and oncogenic mutations have been largely investigated. Up to half of affected patients develop metastases that are the leading single cause of death after diagnosis of UM. Precise systemic therapy addressing metastatic UM and significantly improving the surveillance is not available for each single case. However, identifying predictive factors, achieving international consensus on surveillance protocols, aiming to inactivate micrometastases, and standardizing outcomes would be crucial to be able to effectively cure metastatic UM.

INTRODUCTION

Uveal melanoma (UM) is a rare ocular tumor regarded as the most common primary malignancy in the adult eye. The annual incidence is approximately 6-7 per million in the United States, accounting for 3.7% of all melanomas[1]. UM derives from the pigmented uveal zone, which comprises the choroid, ciliary body, and iris, and is featured by characteristic cytogenetic changes, oncogenic mutations in GNAQ or GNA11, and tropism to aggressively metastasize to the liver resulting in a poor prognosis[2,3]. At this time, UM has no established and effective treatments once metastases arise or have been detected. Although several immunotherapies have demonstrated efficacy in metastatic melanoma of cutaneous origin, these immune-based therapies have disappointing outcomes in UM[3,4]. Some authors have speculated that ocular melanomas, arising from the uveal tract, might be regarded as an immunotherapy-resistant variant of ocular melanomas[5].

Numerous studies in scientific medical literature continually show that tumor-associated cell therapy tends to be an effective alternative and innovative method to fight metastasis. In the last decades, studies have shown that immunotherapies therapies can bring substantial benefits to patients suffering from a wide range of neoplasia and metastatic disease[6,7]. For this reason, huge investments, resources, and important clinical trials have been performed for immunotherapy research and its potential benefit on UM metastatic disease.

Before undertaking this study, we searched PubMed (https://pubmed.ncbi.nlm.nih.gov) and Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com) for the terms "metastatic uveal melanoma" (1788 papers) and "uveal melanoma immunotherapy" (367 papers) for articles published between January 1, 2000, to August 31, 2023. We considered only studies in English, with abstracts and structured text, and those referring to humans, whereas we excluded "case reports", "case series", "conference papers", "letters" and "*in vitro*" studies. The reference lists of all retrieved articles were scanned to detect further relevant papers.

Genetics and pathways involved in UM

Differently from cutaneous melanoma, which usually harbors an activating BRAF (52%) or NRAS (10%-25%) mutation or inactivation of the *NF1* gene, UMs, as well as uveal nevi, are commonly characterized by a mutation in GNAQ or GNA11 [8-10]. These genetic alterations, however, are not sufficient to drive the full malignant transformation to melanoma, being rather an initiating event[11]. GNAQ/11 activates mitogen activating protein kinase (MAPK) pathway, present in most UM, as well as PKC, AKT, and Yes-associated protein 1, associated with tumor growth in some UM models[12,13].

Another genetic pathway implicated in UM involve schromosome 3, specifically the BAP1 tumor suppressor gene. The loss of one copy of chromosome 3 is indeed an established negative prognostic factor associated with metastasis and poor clinical outcome, while BAP1 mutation leads to malignant transformation when associated with chromosome 3 monosomy, as the other gene copy is already lost[14,15].

Immune checkpoint inhibitors

Activation of T cells by antigen-presenting cells (dendritic cells) is the key point of an effective immune reaction against cancer cell antigens. This process is enhanced by co-stimulatory molecules like CD28 and B-7, and hampered by immune checkpoints like cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). These molecules modulate the immune response, preventing inappropriate activation of T cells and controlling excessive immune reaction[16]. CTLA-4, when expressed, binds B-7 with a higher affinity than CD28, thus way blocking CD28-mediated co-stimulation; conversely, PD-1 interacts mainly with programmed death-ligand 1 (PD-L1) and mostly affects the effector phase of the immune response[17].

Immune checkpoint inhibitors (ICIs) are antibodies suppressing the negative immunomodulatory activities of their targets (*i.e.*, CTLA-4 and PD-1). The consequent activation of T cell-mediated response can result in lysis and degradation of cancer cells, ultimately leading to long-term tumor control. This practice-changing concept was first demonstrated by the studies by James P Allison and Tasuku Honjo, awarded the Nobel Prize in Physiology or Medicine in 2018[18].

Malignant melanoma was the first indication for which ipilimumab, an antibody targeting the CTLA-4, was approved by the Food and Drug Administration (FDA) in 2011[19,20]. Few years later, the anti-PD-1 antibodies nivolumab and pembrolizumab were also approved. ICIs have been subsequently tested in metastatic UM (mUM); however, robust conclusions regarding their efficacy are difficult to draw given the many limitations of the available data[21-30].

Anti CTLA-4 antibodies

Ipilimumab, whose efficacy in mUM was evaluated in just a few studies, is a humanized monoclonal antibody blocking the CTLA-4 receptor, enhancing T-cell activation, and amplifying T-cell-mediated immunity. Tremelimumab is an anti-CTLA-4 antibody that has also been proposed for mUM[22]. A recent systematic review and meta-analysis of Pham *et al* [31] showed that the objective response rate (ORR) was 4.1% for anti-CTLA4, with a median overall survival (OS) of 8.0 mo, and a 12-mo OS rate of 34.7%[31]. The progression-free survival (PFS) was longer in treatment-naïve patients than in pretreated patients, with a median value of 3.3 mo. The side effect profile was similar to studies of CTLA-4 inhibitors in cutaneous melanoma, with an overall adverse event (AE) rate of 64.5% and a grade 3-4 AE rate of 17.5% (more commonly hepatitis and diarrhea). No deaths secondary to AEs were reported[32]. Overall, CTLA-4 inhibitors appear to have limited activity in mUM; consequently, their use is generally restricted to selected cases.

Anti PD-1 antibodies

After nivolumab and pembrolizumab were first approved by the FDA for melanoma in 2014, the number of agents acting on the PD-1/PD-L1 axis and their indications across malignancies have been rapidly rising[33]. Concerning mUM, pembrolizumab and nivolumab have been the most studied, but atezolizumab and avelumab have also been proposed [34]. Pham *et al*[31] reported anORR of 7.1% for anti-PD-1 antibodies. Median OS was 11.7 mo, 12-mo OS probability was 48.9%, and PFS was 3.2 mo. These data, similar toanti-CTLA-4 antibodies, suggest that their activity is modest, with only a few patients benefiting from them. Anyway, a better toxicity profile (AE rate of 50.2%; grade 3-4 AE rate of 13.2%) favors them with respect to ipilimumab.

Combined therapies

The dramatic efficacy of the combination of iplimumab and nivolumab in metastatic cutaneous melanoma prompted studies also in mUM: However, as already reported for monotherapies, efficacy was substantially lower[35]. Indeed, the recent meta-analysis of Pham *et al*[31] showed an ORR dropped to 13.5%, with a median OS of 16.0 mo, a 12-mo OS rate of 60.3%, and a median PFS of 3.2 mo. Although these data were slightly better, they are not sufficient to support a clear benefit for mUM patients. Moreover, toxicity is also higher and can be substantial, as shown by an overall AE rate of 85.8% and a grade 3-4 AE rate of 33.9%.

The mechanisms determining a substantially reduced efficacy of ICIs in mUM *vs* metastatic cutaneous melanoma are not completely understood. The studies have shown an immune privilege of UM inside the eye through multiple strategies, including expression of PD-L1 and indoleamine dioxygenase-1: These are also allegedly active at metastatic deposits, particularly in the liver, creating a microenvironment particularly resistant to immunotherapy. A low tumor mutational burden has also been suggested to contribute[36,37].

ICIs in combination with liver-directed therapies

The liver is the most common site for UM metastases, and about 50% of the patients will have isolated liver metastases. High lactate dehydrogenase and liver metastases are dominant predictors for ICI failure in cancer therapy since hepatic disease in mUM is particularly resistant to immunotherapy[38]. Therefore, liver-directed therapies in combination with ICIs have a strong rationale.

Treatment with ipilimumab/nivolumab in combination with percutaneous hepatic perfusion with melphalan has been explored in a phase Ibtrialona small number of patients. The authors found 1 complete response, 5 partial responses, and 1 stable disease. Grade III/IV AEs were observed in 5/7 patients without dose-limiting toxicities or death[39].

Minor *et al*[40] conducted a pilot study on 26 patients with hepatic metastases of UM treated with two cycles of selective internal radiation therapy (SIRT) with yttrium-90 (90Y) resin microspheres, one to each lobe of the liver, followed in 2-4 wk by immunotherapy with ipilimumab/nivolumab every 3 wk for four doses, then maintenance immunotherapy with nivolumab alone. Initial dosing of both 90Y and immunotherapy resulted in excessive toxicity but, after decreasing the dosage of 90Y microspheres to limit the radiation dose to normal liver to 35 Gy and lowering the ipilimumab dose to 1 mg/kg, the treatment was tolerable. Reported ORR was 20%, median OS 15 mo, and median PFS 5.5 mo[40].

Aedo-Lopez *et al*[41] conducted a retrospective study of 32 patients with mUM divided into two groups based on the treatment received: SIRT with 90Y microspheres and ipilimumab/nivolumab before or after the SIRT (18 patients) *vs* SIRT without combined immunotherapy (14 patients). Median OS was 49.6 and 13.6 mo in the two groups respectively. The presence of extra hepatic-metastases at the time of SIRT, a liver lesion over 8 cm, and a high liver tumor volume negatively impacted survival[41].

A case series of 8 patients treated with ipilimumab/nivolumab combination along with transarterial chemoembolization (TACE), followed by nivolumab maintenance and monthly TACE procedures, demonstrated a median OS of 14.2 mo. Two/8 patients had partial response, 4/8 stable disease, 2/8 disease progression[42]. A phase Ib/II study was conducted to assess the safety and efficacy of radiofrequency ablation (RFA) of one liver metastatic lesion plus ipilimumab. Recommended phase II dose was ipilimumab 3 mg/kg + RFA. No confirmed objective responses were observed. Median OS was 14.2 mo for the 10 mg/kg ipilimumab cohort *vs* 9.7 mo for the 3 mg/kg cohort. Median PFS

was 3 mo comparable for both cohorts. Combining RFA with ipilimumab 3 mg/kg was well tolerated but showed very limited clinical activity in UM[43].

An ongoing phase II trial (NCT03472586) studies ipilimumab and nivolumab in combination with immunoembolization with lipiodol and granulocyte-macrophage colony-stimulating factor in patients with liver metastases from UM. Similarly, a phase I randomized controlled multicenter trial (NCT04463368) is evaluating the effectiveness of isolated hepatic perfusion with melphalan in combination with ipilimumab and nivolumab. The isolation of the liver from the systemic circulation allows a high concentration of the chemotherapeutic agent to be delivered to the liver in conjunction with hyperthermia, allowing a higher efficacy with minimal systemic exposure to the drug.

Other strategies

The phase Ib, open-label CLEVER study evaluated treatment with intravenous coxsackievirus A21 (V937) in combination with ipilimumab in patients with mUM, based on the rationale that the combination of V937 and ipilimumab might result in augmented T-cell responses with consequent improved clinical activity. However, the combination regimen did not result in objective responses, although 3 patients obtained a stable disease[44].

Drugs targeting epigenetic regulators such as histone deacetylases (HDACs) show promise as cancer therapies by reversing oncogene transcription and modifying the tumor microenvironment. A phase II trial was conducted to evaluate if anti-PD-1 therapies and HDAC inhibitors (entinostat) could synergize. ORR was 14%, median OS was 13.4 mo and median PFS was 2.1 mo, slightly higher than that of anti-PD-1 monotherapy[45]. Arginine deprivation with ADI PEG-20 with ipilimumab/nivolumab was also studied in a phase I trial; however, there were no objective responses, and the median OS was only 8.6 mo[46].

Lymphocyte-activation gene 3 (LAG-3) is another immune checkpoint that negatively regulates T-cell proliferation and effector T-cell function. LAG-3 and PD-1 are often co-expressed on tumor-infiltrating lymphocytes, thus contributing to tumor-mediated T-cell exhaustion: Upon this rationale, the phase III RELATIVITY-047 trial validated LAG-3 blockade as a relevant biological target and established it as the third clinically relevant immune checkpoint, demonstrating improved antitumor activity for the combination of the anti-LAG-3 antibody relatlimab and nivolumab concerning nivolumab alone [47]. After these results, the combination nivolumab/relatlimab (Opdualag) was approved for medical use in the United States in March 2022 for the first-line therapy of patients with metastatic melanoma. Whether the combination is effective also in rare melanoma subtypes remains to be elucidated: An ongoing trial (NCT04552223) aims to test it in mUM patients. A study from a southern French patient cohort confirmed LAG-3 and PRAME (PReferentially expressed Antigen in MElanoma) as potentially important immunotherapy targets in the treatment of UM patients while proposing V-domain Ig suppressor of T-cell activation as a novel relevant immune checkpoint molecule in primary UM[48].

Immunotherapy has proven to be an interesting and viable option in UM metastatic disease, even though much has still to be studied to have scientific and clinical effectiveness. Despite optimal management of primary tumors, about half of patients will eventually develop distant metastatic disease. Differently from cutaneous melanoma, the liver is involved in the vast majority of cases: This led to the employment of liver-directed therapies with encouraging results in carefully selected patients[49]. However, a randomized trial comparing hepatic artery infusion *vs* systemic fotemustine was stopped early for futility after failure to show improved OS despite improvement in PFS[50]. This observation, considering also that most patients either progress after or are not candidates for locoregional therapy, suggests that effective systemic treatments may represent the therapeutic mainstay.

Historically, patients with ocular or UM were excluded from clinical trials on cutaneous melanoma because of the biological and clinical differences: Therefore, there has been no widely accepted standard treatment, and patients were generally managed with drugs and regimens approved for cutaneous melanoma (*i.e.,* dacarbazine, temozolomide, or fotemustine). However, despite some responses being observed, none of them was demonstrated to be effective[51].

The discovery of the presence of activating mutation in GNAQ/GNA11 in the majority of UM patients, resulting in constitutional activation of MAPK pathways, led to the development of the MEK inhibitor selumetinib in this setting. A first randomized, phase II clinical trial compared it with chemotherapy (dacarbazine or temozolomide); the primary endpoint was PFS. Selumetinib improved PFS concerning the comparator, but the AE rate was high and OS was similar between the two arms[52]. A subsequent randomized, placebo-controlled, phase III study evaluated its combination with dacarbazine concerning dacarbazine monotherapy and failed to show any improvement in either PFS or OS[53].

The ICIs proved very effective in cutaneous melanoma and were subsequently tested in ocular melanoma; however, the results were not as good as expected. Despite retrospective reports suggesting potential efficacy ipilimumab, an anti-CTLA4 antibody, did not show any response in a phase II clinical trial; PFS and OS were comparable with historical controls treated with chemotherapy[54].

The anti-PD1 agents nivolumab and pembrolizumab were also tested as monotherapies in phase II clinical trials. Both agents showed clinical responses that were sometimes durable; however, PFS and OS were highly variable and, overall, not so different from those obtained with chemotherapy[55]. Other two studies evaluated the combination of ipilimumab and nivolumab, after the very good results observed in cutaneous melanoma. A first study on 55 patients showed a high rate (51.9%) of disease stabilization; however, PFS and OS were still comparable to historical controls treated with chemotherapy[56]. Data from the second one were more promising, observing a median PFS of 5.5 mo and OS of 19.1 mo, but only 33 patients were evaluable for efficacy[57]. Overall, these data demonstrate that ICIs, and especially the combination of ipilimumab and nivolumab, may achieve durable responses, but with a limited prognostic impact.

Tebentafusp

ImmTAC, short for immune-mobilizing monoclonal T-cell receptors against cancer, represents a novel category of T-cell–redirecting bispecific fusion proteins. These innovative molecules utilize an engineered high-affinity T-cell receptor to effectively target any protein, including intracellular antigens, displayed as a peptide-HLA complex on the surface of

Table 1 Drug therapies for metastatic uveal melanoma disease

Drug	Target	Action
Ipilimumab	CTLA-4	Blocking the CTLA-4 receptor, enhancing T-cell activation, amplifying T-cell-mediated immunity
Tremelimumab	CTLA-4	Blocking the CTLA-4 receptor, amplifying T-cell-mediated immunity
Nivolumab	PD-1	Activation of T cell-mediated response. Lysis and degradation of cancer cells
Pembrolizumab	PD-1	Activation of T cell-mediated response. Lysis and degradation of cancer cells
Coxsackievirus A21 (V937)		Augmented T-cell responses with consequent improved clinical activity
Lymphocyte-activation gene 3		Negatively regulation T-cell proliferation and effector T-cell function
Tebentafusp	T-cell-redirecting bispecific fusion proteins	Enhancing HLA-A∗0201-restricted T-cell receptor specifically recognizing the glycoprotein 100

CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; PD-1: Programmed cell death protein 1.

the target cell[58]. Tebentafusp, previously known as IMCgp100, is an example of such a molecule, featuring a soluble, enhanced HLA-A∗0201-restricted T-cell receptor specifically recognizing the glycoprotein 100 (gp100) peptide YLEPGPVTA, that is highly express on UM cells. This receptor is fused with an anti-CD3 single-chain variable fragment. When the ImmTAC binds to its designated peptide–HLA complexes on the surface of the target cell, it enlists and stimulates polyclonal T cells *via* CD3, to kill these cells. In addition to its T cell cytotoxic effects, IMCgp100 stimulates T cells to secrete a diverse array of cytokines and chemokines, such as interleukin-6 (IL-6), IL-2, and tumor necrosis factor-alpha, thereby amplifying its potential as an anti-cancer immune agent[59,60]. The activation of T-cells by IMCgp100 occurs at a concentration of 1 pM, with the most significant reaction observed at 1 nM. Off-target effects are observable solely at concentrations significantly exceeding 1 nM, highlighting the high specificity of the tumor antigen and a broad therapeutic range, and IMCgp100 activity *in vitro* correlates with the cellular expression levels of gp100-HLA-A∗01[61].

The drug was tested in a phase III randomized trial (2:1) against a comparator chosen by the investigator among pembrolizumab, ipilimumab, or dacarbazine (Table 1). PFS was not significantly different among the two arms, but OS was superior in the tebentafusp arm (21.7 *vs* 16 mo; hazard ratio = 0.51). The decoupling between PFS and OS was explained by the observation that, while responding patients had similar outcomes in both arms, the prognosis of unresponsive patients was better in the tebentafusp arm, suggesting that treatment-induced immune activation slows disease progression even in the absence of an objective response. The toxicity observed is mild or moderate in most cases, with the cytokine-release syndrome and cutaneous reaction being the most characteristic drug-related AEs[62].

Tebentafusp has undoubtedly marked a significant advancement in the treatment of metastatic UM, offering a survival benefit over conventional therapies. Its preferential binding to HLA-A0201 has limited its applicability to patients with this specific subtype, prompting a need for the development of alternative treatments for individuals with other HLA subtypes. Although subgroup analyses in the phase III trial raised questions regarding its potential efficacy in certain patient groups, including those with high tumor burden and poorer performance status, its overall benefit still positions it as a preferred therapeutic option for most HLA-A0201-positive patients. Regarding the optimal duration of treatment, current data suggest that continuing tebentafusp until confirmed radiological progression might be a reasonable approach, given its manageable and predictable toxicities. However, more extensive studies are required to establish the most suitable duration for treatment. Additionally, the challenge of evaluating treatment response necessitates the exploration of alternative markers beyond traditional response measures. The correlation between rash appearance and improved survival warrants further investigation, while circulating tumor DNA reduction holds promise as a potential indicator of treatment benefit.

The investigation of tebentafusp in conjunction with liver-directed therapies is also a significant area of interest, considering the potential benefit for patients with bulky disease. Furthermore, the exploration of other therapeutic targets, such as PRAME, through alternative treatments like IMC-F106C, presents a promising direction for future research efforts.

In this scenario, while certain limitations exist, tebentafusp represents a groundbreaking development in the field of metastatic UM treatment. Unanswered questions regarding response monitoring and application in diverse treatment settings warrant further exploration to optimize its therapeutic potential and expand its applicability to a broader patient population. Future research objectives should include the determination of theoptimal treatment sequence between tebentafusp and checkpoint blockade, as well as the potential benefits of combining these therapies. Ongoing studies focusing on the combination of tebentafusp with other immunotherapies and the assessment of its role in the adjuvant setting after primary disease therapy are critical in further delineating its therapeutic scope. Further research and a comprehensive understanding of tebentafusp's mechanisms will undoubtedly pave the way for improved treatment strategies and outcomes in the management of metastatic UM.

CONCLUSION

To conclude, research on immunotherapy for UM metastatic disease has vast supporting scientific and clinically applicable literature but is just at the beginning of a new era for effective treatment to practically increase the surveillance of affected patients. Predictive biomarkers, mechanisms of resistance, treatment duration and treatment beyond progression, immune-related toxicities, and clinical trial design are key concepts in need of further consideration to optimize the anticancer potential treatments. Future studies based on longer follow-up with homogenous criteria, preferably on human subjects, can pave the way to tailoring immunotherapy for patients affected by ultraviolet metastatic disease.

FOOTNOTES

REFERENCES

1   **Krantz BA**, Dave N, Komatsubara KM, Marr BP, Carvajal RD. Uveal melanoma: epidemiology, etiology, and treatment of primary disease. *Clin Ophthalmol* 2017; **11**: 279-289 [PMID: 28203054 DOI: 10.2147/OPTH.S89591]

2   **Chattopadhyay C**, Kim DW, Gombos DS, Oba J, Qin Y, Williams MD, Esmaeli B, Grimm EA, Wargo JA, Woodman SE, Patel SP. Uveal melanoma: From diagnosis to treatment and the science in between. *Cancer* 2016; **122**: 2299-2312 [PMID: 26991400 DOI: 10.1002/cncr.29727]

3   **Jager MJ**, Shields CL, Cebulla CM, Abdel-Rahman MH, Grossniklaus HE, Stern MH, Carvajal RD, Belfort RN, Jia R, Shields JA, Damato BE. Uveal melanoma. *Nat Rev Dis Primers* 2020; **6**: 24 [PMID: 32273508 DOI: 10.1038/s41572-020-0158-0]

4   **Rossi E**, Croce M, Reggiani F, Schinzari G, Ambrosio M, Gangemi R, Tortora G, Pfeffer U, Amaro A. Uveal Melanoma Metastasis. *Cancers (Basel)* 2021; **13** [PMID: 34830841 DOI: 10.3390/cancers13225684]

5   **Chandran SS**, Somerville RPT, Yang JC, Sherry RM, Klebanoff CA, Goff SL, Wunderlich JR, Danforth DN, Zlott D, Paria BC, Sabesan AC, Srivastava AK, Xi L, Pham TH, Raffeld M, White DE, Toomey MA, Rosenberg SA, Kammula US. Treatment of metastatic uveal melanoma with adoptive transfer of tumour-infiltrating lymphocytes: a single-centre, two-stage, single-arm, phase 2 study. *Lancet Oncol* 2017; **18**: 792-802 [PMID: 28395880 DOI: 10.101/S1470-2045(17)30251-6]

6   **Feng X**, Arang N, Rigiracciolo DC, Lee JS, Yeerna H, Wang Z, Lubrano S, Kishore A, Pachter JA, König GM, Maggiolini M, Kostenis E, Schlaepfer DD, Tamayo P, Chen Q, Ruppin E, Gutkind JS. A Platform of Synthetic Lethal Gene Interaction Networks Reveals that the GNAQ Uveal Melanoma Oncogene Controls the Hippo Pathway through FAK. *Cancer Cell* 2019; **35**: 457-472.e5 [PMID: 30773340 DOI: 10.1016/j.ccell.2019.01.009]

7   **Fu Y**, Xiao W, Mao Y. Recent Advances and Challenges in Uveal Melanoma Immunotherapy. *Cancers (Basel)* 2022; **14** [PMID: 35804863 DOI: 10.3390/cancers14133094]

8   **Bauer J**, Kilic E, Vaarwater J, Bastian BC, Garbe C, de Klein A. Oncogenic GNAQ mutations are not correlated with disease-free survival in uveal melanoma. *Br J Cancer* 2009; **101**: 813-815 [PMID: 19654573 DOI: 10.1038/sj.bjc.6605226]

9   **Jensen DE**, Rauscher FJ 3rd. BAP1, a candidate tumor suppressor protein that interacts with BRCA1. *Ann N Y Acad Sci* 1999; **886**: 191-194 [PMID: 10667217 DOI: 10.1111/j.1749-6632.1999.tb09414.x]

10   **Davies H**, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA. Mutations of the BRAF gene in human cancer. *Nature* 2002; **417**: 949-954 [PMID: 12068308 DOI: 10.1038/nature00766]

11   **Van Raamsdonk CD**, Bezrookove V, Green G, Bauer J, Gaugler L, O'Brien JM, Simpson EM, Barsh GS, Bastian BC. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature* 2009; **457**: 599-602 [PMID: 19078957 DOI: 10.1038/nature07586]

12   **Feng X**, Degese MS, Iglesias-Bartolome R, Vaque JP, Molinolo AA, Rodrigues M, Zaidi MR, Ksander BR, Merlino G, Sodhi A, Chen Q, Gutkind JS. Hippo-independent activation of YAP by the GNAQ uveal melanoma oncogene through a trio-regulated rho GTPase signaling circuitry. *Cancer Cell* 2014; **25**: 831-845 [PMID: 24882515 DOI: 10.1016/j.ccr.2014.04.016]

13   **Vaqué JP**, Dorsam RT, Feng X, Iglesias-Bartolome R, Forsthoefel DJ, Chen Q, Debant A, Seeger MA, Ksander BR, Teramoto H, Gutkind JS. A genome-wide RNAi screen reveals a Trio-regulated Rho GTPase circuitry transducing mitogenic signals initiated by G protein-coupled receptors. *Mol Cell* 2013; **49**: 94-108 [PMID: 23177739 DOI: 10.1016/j.molcel.2012.10.018]

14   **Scholes AG**, Damato BE, Nunn J, Hiscott P, Grierson I, Field JK. Monosomy 3 in uveal melanoma: correlation with clinical and histologic predictors of survival. *Invest Ophthalmol Vis Sci* 2003; **44**: 1008-1011 [PMID: 12601021 DOI: 10.1167/iovs.02-0159]

15   **Harbour JW**, Onken MD, Roberson ED, Duan S, Cao L, Worley LA, Council ML, Matatall KA, Helms C, Bowcock AM. Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science* 2010; **330**: 1410-1413 [PMID: 21051595 DOI: 10.1126/science.1194472]

16   **Han Y**, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. *Am J Cancer Res* 2020; **10**: 727-742 [PMID: 32266087]

17   **Salmaninejad A**, Valilou SF, Shabgah AG, Aslani S, Alimardani M, Pasdar A, Sahebkar A. PD-1/PD-L1 pathway: Basic biology and role in cancer immunotherapy. *J Cell Physiol* 2019; **234**: 16824-16837 [PMID: 30784085 DOI: 10.1002/jcp.28358]

18   **Ljunggren HG**, Jonsson R, Höglund P. Seminal immunologic discoveries with direct clinical implications: The 2018 Nobel Prize in Physiology or Medicine honours discoveries in cancer immunotherapy. *Scand J Immunol* 2018; **88**: e12731 [PMID: 30485497 DOI: 10.1111/sji.12731]

19   **Beaver JA**, Tzou A, Blumenthal GM, McKee AE, Kim G, Pazdur R, Philip R. An FDA Perspective on the Regulatory Implications of Complex Signatures to Predict Response to Targeted Therapies. *Clin Cancer Res* 2017; **23**: 1368-1372 [PMID: 27993967 DOI: 10.1158/1078-0432.CCR-16-1098]

20   **Davis AA**, Patel VG. The role of PD-L1 expression as a predictive biomarker: an analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. *J Immunother Cancer* 2019; **7**: 278 [PMID: 31655605 DOI: 10.1186/s40425-019-0768-9]

21   **Maio M**, Danielli R, Chiarion-Sileni V, Pigozzo J, Parmiani G, Ridolfi R, De Rosa F, Del Vecchio M, Di Guardo L, Queirolo P, Picasso V, Marchetti P, De Galitiis F, Mandalà M, Guida M, Simeone E, Ascierto PA. Efficacy and safety of ipilimumab in patients with pre-treated, uveal melanoma. *Ann Oncol* 2013; **24**: 2911-2915 [PMID: 24067719 DOI: 10.1093/annonc/mdt376]

22   **Joshua AM**, Monzon JG, Mihalcioiu C, Hogg D, Smylie M, Cheng T. A phase 2 study of tremelimumab in patients with advanced uveal melanoma. *Melanoma Res* 2015; **25**: 342-347 [PMID: 26050146 DOI: 10.1097/CMR.0000000000000175]

23   **Karydis I**, Chan PY, Wheater M, Arriola E, Szlosarek PW, Ottensmeier CH. Clinical activity and safety of Pembrolizumab in Ipilimumab pre-treated patients with uveal melanoma. *Oncoimmunology* 2016; **5**: e1143997 [PMID: 27467964 DOI: 10.1080/2162402X.2016.1143997]

24   **Kirchberger MC**, Moreira A, Erdmann M, Schuler G, Heinzerling L. Real world experience in low-dose ipilimumab in combination with PD-1 blockade in advanced melanoma patients. *Oncotarget* 2018; **9**: 28903-28909 [PMID: 29988983 DOI: 10.18632/oncotarget.25627]

25   **Heppt MV**, Amaral T, Kähler KC, Heinzerling L, Hassel JC, Meissner M, Kreuzberg N, Loquai C, Reinhardt L, Utikal J, Dabrowski E, Gesierich A, Pföhler C, Terheyden P, Thoms KM, Zimmer L, Eigentler TK, Kirchberger MC, Stege HM, Meier F, Schlaak M, Berking C. Combined immune checkpoint blockade for metastatic uveal melanoma: a retrospective, multi-center study. *J Immunother Cancer* 2019; **7**: 299 [PMID: 31722735 DOI: 10.1186/s40425-019-0800-0]

26   **Johnson DB**, Bao R, Ancell KK, Daniels AB, Wallace D, Sosman JA, Luke JJ. Response to Anti-PD-1 in Uveal Melanoma Without High-Volume Liver Metastasis. *J Natl Compr Canc Netw* 2019; **17**: 114-117 [PMID: 30787124 DOI: 10.6004/jnccn.2018.7070]

27   **Rossi E**, Pagliara MM, Orteschi D, Dosa T, Sammarco MG, Caputo CG, Petrone G, Rindi G, Zollino M, Blasi MA, Cassano A, Bria E, Tortora G, Schinzari G. Pembrolizumab as first-line treatment for metastatic uveal melanoma. *Cancer Immunol Immunother* 2019; **68**: 1179-1185 [PMID: 31175402 DOI: 10.1007/s00262-019-02352-6]

28   **Namikawa K**, Takahashi A, Mori T, Tsutsumida A, Suzuki S, Motoi N, Jinnai S, Kage Y, Mizuta H, Muto Y, Nakano E, Yamazaki N. Nivolumab for patients with metastatic uveal melanoma previously untreated with ipilimumab: a single-institution retrospective study. *Melanoma Res* 2020; **30**: 76-84 [PMID: 31095037 DOI: 10.1097/CMR.0000000000000617]

29   **Piulats JM**, Espinosa E, de la Cruz Merino L, Varela M, Alonso Carrión L, Martín-Algarra S, López Castro R, Curiel T, Rodríguez-Abreu D, Redrado M, Gomà M, Rullán AJ, Calvo González A, Berrocal-Jaime A. Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402). *J Clin Oncol* 2021; **39**: 586-598 [PMID: 33417511 DOI: 10.1200/JCO.20.00550]

30   **Salaün H**, de Koning L, Saint-Ghislain M, Servois V, Ramtohul T, Garcia A, Matet A, Cassoux N, Mariani P, Piperno-Neumann S, Rodrigues M. Nivolumab plus ipilimumab in metastatic uveal melanoma: a real-life, retrospective cohort of 47 patients. *Oncoimmunology* 2022; **11**: 2116845 [PMID: 36092639 DOI: 10.1080/2162402X.2022.2116845]

31   **Pham JP**, On L, Ardolino L, Hurwitz J, Salaun H, Sim HW, Joshua AM. Efficacy of immune checkpoint inhibition in metastatic uveal melanoma: a systematic review and meta-analysis. *Melanoma Res* 2023; **33**: 316-325 [PMID: 37199712 DOI: 10.1097/CMR.0000000000000900]

32   **Larkin J**, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, Cowey CL, Schadendorf D, Wagstaff J, Dummer R, Ferrucci PF, Smylie M, Hogg D, Hill A, Márquez-Rodas I, Haanen J, Guidoboni M, Maio M, Schöffski P, Carlino MS, Lebbé C, McArthur G, Ascierto PA, Daniels GA, Long GV, Bastholt L, Rizzo JI, Balogh A, Moshyk A, Hodi FS, Wolchok JD. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med* 2019; **381**: 1535-1546 [PMID: 31562797 DOI: 10.1056/NEJMoa1910836]

33   **Gong J**, Chehrazi-Raffle A, Reddi S, Salgia R. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations. *J Immunother Cancer* 2018; **6**: 8 [PMID: 29357948 DOI: 10.1186/s40425-018-0316-z]

34   **Keilholz U**, Mehnert JM, Bauer S, Bourgeois H, Patel MR, Gravenor D, Nemunaitis JJ, Taylor MH, Wyrwicz L, Lee KW, Kasturi V, Chin K, von Heydebreck A, Gulley JL. Avelumab in patients with previously treated metastatic melanoma: phase 1b results from the JAVELIN Solid Tumor trial. *J Immunother Cancer* 2019; **7**: 12 [PMID: 30651126 DOI: 10.1186/s40425-018-0459-y]

35   **Wolchok JD**, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, Lao CD, Wagstaff J, Schadendorf D, Ferrucci PF, Smylie M, Dummer R, Hill A, Hogg D, Haanen J, Carlino MS, Bechter O, Maio M, Marquez-Rodas I, Guidoboni M, McArthur G, Lebbé C, Ascierto PA, Long GV, Cebon J, Sosman J, Postow MA, Callahan MK, Walker D, Rollin L, Bhore R, Hodi FS, Larkin J. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med* 2017; **377**: 1345-1356 [PMID: 28889792 DOI: 10.1056/NEJMoa1709684]

36   **Luke JJ**, Triozzi PL, McKenna KC, Van Meir EG, Gershenwald JE, Bastian BC, Gutkind JS, Bowcock AM, Streicher HZ, Patel PM, Sato T, Sossman JA, Sznol M, Welch J, Thurin M, Selig S, Flaherty KT, Carvajal RD. Biology of advanced uveal melanoma and next steps for clinical therapeutics. *Pigment Cell Melanoma Res* 2015; **28**: 135-147 [PMID: 25113308 DOI: 10.1111/pcmr.12304]

37   **Rothermel LD**, Sabesan AC, Stephens DJ, Chandran SS, Paria BC, Srivastava AK, Somerville R, Wunderlich JR, Lee CC, Xi L, Pham TH, Raffeld M, Jailwala P, Kasoji M, Kammula US. Identification of an Immunogenic Subset of Metastatic Uveal Melanoma. *Clin Cancer Res* 2016; **22**: 2237-2249 [PMID: 26712692 DOI: 10.1158/1078-0432.CCR-15-2294]

38   **Dercle L**, Ammari S, Roblin E, Bigorgne A, Champiat S, Taihi L, Plaian A, Hans S, Lakiss S, Tselikas L, Rouanne M, Deutsch E, Schwartz LH, Gönen M, Flynn J, Massard C, Soria JC, Robert C, Marabelle A. High serum LDH and liver metastases are the dominant predictors of primary cancer resistance to anti-PD(L)1 immunotherapy. *Eur J Cancer* 2022; **177**: 80-93 [PMID: 36332438 DOI: 10.1016/j.ejca.2022.08.034]

39   **Tong TML**, Burgmans MC, Speetjens FM, van Erkel AR, van der Meer RW, van Rijswijk CSP, Jonker-Bos MA, Roozen CFM, Sporrel-Blokland M, Lutjeboer J, van Persijn van Meerten EL, Martini CH, Zoethout RWM, Tijl FGJ, Blank CU, Kapiteijn E. Combining Melphalan Percutaneous Hepatic Perfusion with Ipilimumab Plus Nivolumab in Advanced Uveal Melanoma: First Safety and Efficacy Data from the Phase Ib Part of the Chopin Trial. *Cardiovasc Intervent Radiol* 2023; **46**: 350-359 [PMID: 36624292 DOI: 10.1007/s00270-022-03338-1]

40   **Minor DR**, Kim KB, Tong RT, Wu MC, Kashani-Sabet M, Orloff M, Eschelman DJ, Gonsalves CF, Adamo RD, Anne PR, Luke JJ, Char D, Sato T. A Pilot Study of Hepatic Irradiation with Yttrium-90 Microspheres Followed by Immunotherapy with Ipilimumab and Nivolumab for Metastatic Uveal Melanoma. *Cancer Biother Radiopharm* 2022; **37**: 11-16 [PMID: 35021863 DOI: 10.1089/cbr.2021.0366]

41   **Aedo-Lopez V**, Gérard CL, Boughdad S, Gautron Moura B, Berthod G, Digklia A, Homicsko K, Schaefer N, Duran R, Cuendet MA, Michielin O. Safety and Efficacy of Ipilimumab plus Nivolumab and Sequential Selective Internal Radiation Therapy in Hepatic and Extrahepatic Metastatic Uveal Melanoma. *Cancers (Basel)* 2022; **14** [PMID: 35267470 DOI: 10.3390/cancers14051162]

42   **Karivedu V**, Eldessouki I, Taftaf A, Zhu Z, Makramalla A, Karim NA. Nivolumab and Ipilimumab in the Treatment of Metastatic Uveal Melanoma: A Single-Center Experience. *Case Rep Oncol Med* 2019; **2019**: 3560640 [PMID: 31179139 DOI: 10.1155/2019/3560640]

43   **Rozeman EA**, Prevoo W, Meier MAJ, Sikorska K, Van TM, van de Wiel BA, van der Wal JE, Mallo HA, Grijpink-Ongering LG, Broeks A, Lalezari F, Reeves J, Warren S, van Thienen JV, van Tinteren H, Haanen JBAG, Kapiteijn E, Blank CU. Phase Ib/II trial testing combined radiofrequency ablation and ipilimumab in uveal melanoma (SECIRA-UM). *Melanoma Res* 2020; **30**: 252-260 [PMID: 31895753 DOI: 10.1097/CMR.0000000000000653]

44   **Lutzky J**, Sullivan RJ, Cohen JV, Ren Y, Li A, Haq R. Phase 1b study of intravenous coxsackievirus A21 (V937) and ipilimumab for patients with metastatic uveal melanoma. *J Cancer Res Clin Oncol* 2023; **149**: 6059-6066 [PMID: 36651961 DOI: 10.1007/s00432-022-04510-3]

45   **Ny L**, Jespersen H, Karlsson J, Alsén S, Filges S, All-Eriksson C, Andersson B, Carneiro A, Helgadottir H, Levin M, Ljuslinder I, Olofsson Bagge R, Sah VR, Stierner U, Ståhlberg A, Ullenhag G, Nilsson LM, Nilsson JA. The PEMDAC phase 2 study of pembrolizumab and entinostat in patients with metastatic uveal melanoma. *Nat Commun* 2021; **12**: 5155 [PMID: 34453044 DOI: 10.1038/s41467-021-25332-w]

46   **Kraehenbuehl L**, Holland A, Armstrong E, O'Shea S, Mangarin L, Chekalil S, Johnston A, Bomalaski JS, Erinjeri JP, Barker CA, Francis JH, Wolchok JD, Merghoub T, Shoushtari AN. Pilot Trial of Arginine Deprivation Plus Nivolumab and Ipilimumab in Patients with Metastatic Uveal Melanoma. *Cancers (Basel)* 2022; **14** [PMID: 35681616 DOI: 10.3390/cancers14112638]

47   **Tawbi HA**, Schadendorf D, Lipson EJ, Ascierto PA, Matamala L, Castillo Gutiérrez E, Rutkowski P, Gogas HJ, Lao CD, De Menezes JJ, Dalle S, Arance A, Grob JJ, Srivastava S, Abaskharoun M, Hamilton M, Keidel S, Simonsen KL, Sobiesk AM, Li B, Hodi FS, Long GV; RELATIVITY-047 Investigators. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. *N Engl J Med* 2022; **386**: 24-34 [PMID: 34986285 DOI: 10.1056/NEJMoa2109970]

48   **Lamas NJ**, Lassalle S, Martel A, Nahon-Estève S, Macocco A, Zahaf K, Lalvee S, Fayada J, Lespinet-Fabre V, Bordone O, Pedeutour F, Baillif S, Hofman P. Characterisation of the protein expression of the emerging immunotherapy targets VISTA, LAG-3 and PRAME in primary uveal melanoma: insights from a southern French patient cohort. *Pathology* 2023; **55**: 929-944 [PMID: 37863710 DOI: 10.1016/j.pathol.2023.08.003]

49   **Khan SA**, Almalki WH, Arora S, Kesharwani P. Recent approaches for the treatment of uveal melanoma: Opportunities and challenges. *Crit Rev Oncol Hematol* 2023; **193**: 104218 [PMID: 38040071 DOI: 10.1016/j.critrevonc.2023.104218]

50   **Leyvraz S**, Piperno-Neumann S, Suciu S, Baurain JF, Zdzienicki M, Testori A, Marshall E, Scheulen M, Jouary T, Negrier S, Vermorken JB, Kaempgen E, Durando X, Schadendorf D, Gurunath RK, Keilholz U. Hepatic intra-arterial versus intravenous fotemustine in patients with liver metastases from uveal melanoma (EORTC 18021): a multicentric randomized trial. *Ann Oncol* 2014; **25**: 742-746 [PMID: 24510314 DOI: 10.1093/annonc/mdt585]

51   **Carvajal RD**, Schwartz GK, Tezel T, Marr B, Francis JH, Nathan PD. Metastatic disease from uveal melanoma: treatment options and future prospects. *Br J Ophthalmol* 2017; **101**: 38-44 [PMID: 27574175 DOI: 10.1136/bjophthalmol-2016-309034]

52   **Carvajal RD**, Sosman JA, Quevedo JF, Milhem MM, Joshua AM, Kudchadkar RR, Linette GP, Gajewski TF, Lutzky J, Lawson DH, Lao CD, Flynn PJ, Albertini MR, Sato T, Lewis K, Doyle A, Ancell K, Panageas KS, Bluth M, Hedvat C, Erinjeri J, Ambrosini G, Marr B, Abramson DH, Dickson MA, Wolchok JD, Chapman PB, Schwartz GK. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. *JAMA* 2014; **311**: 2397-2405 [PMID: 24938562 DOI: 10.1001/jama.2014.6096]

53   **Carvajal RD**, Piperno-Neumann S, Kapiteijn E, Chapman PB, Frank S, Joshua AM, Piulats JM, Wolter P, Cocquyt V, Chmielowski B, Evans TRJ, Gastaud L, Linette G, Berking C, Schachter J, Rodrigues MJ, Shoushtari AN, Clemett D, Ghiorghiu D, Mariani G, Spratt S, Lovick S, Barker P, Kilgour E, Lai Z, Schwartz GK, Nathan P. Selumetinib in Combination With Dacarbazine in Patients With Metastatic Uveal Melanoma: A Phase III, Multicenter, Randomized Trial (SUMIT). *J Clin Oncol* 2018; **36**: 1232-1239 [PMID: 29528792 DOI: 10.1200/JCO.2017.74.1090]

54   **Zimmer L**, Vaubel J, Mohr P, Hauschild A, Utikal J, Simon J, Garbe C, Herbst R, Enk A, Kämpgen E, Livingstone E, Bluhm L, Rompel R, Griewank KG, Fluck M, Schilling B, Schadendorf D. Phase II DeCOG-study of ipilimumab in pretreated and treatment-naïve patients with metastatic uveal melanoma. *PLoS One* 2015; **10**: e0118564 [PMID: 25761109 DOI: 10.1371/journal.pone.0118564]

55   **Petzold A**, Steeb T, Wessely A, Koch EAT, Vera J, Berking C, Heppt MV. Is tebentafusp superior to combined immune checkpoint blockade and other systemic treatments in metastatic uveal melanoma? A comparative efficacy analysis with population adjustment. *Cancer Treat Rev* 2023; **115**: 102543 [PMID: 36931146 DOI: 10.1016/j.ctrv.2023.102543]

56   **Seth R**, Agarwala SS, Messersmith H, Alluri KC, Ascierto PA, Atkins MB, Bollin K, Chacon M, Davis N, Faries MB, Funchain P, Gold JS, Guild S, Gyorki DE, Kaur V, Khushalani NI, Kirkwood JM, McQuade JL, Meyers MO, Provenzano A, Robert C, Santinami M, Sehdev A, Sondak VK, Spurrier G, Swami U, Truong TG, Tsai KK, van Akkooi A, Weber J. Systemic Therapy for Melanoma: ASCO Guideline Update. *J Clin Oncol* 2023; **41**: 4794-4820 [PMID: 37579248 DOI: 10.1200/JCO.23.01136]

57   **Lowe KL**, Cole D, Kenefeck R, OKelly I, Lepore M, Jakobsen BK. Novel TCR-based biologics: mobilising T cells to warm 'cold' tumours.

Cancer Treat Rev 2019; **77**: 35-43 [PMID: 31207478 DOI: 10.1016/j.ctrv.2019.06.001]

58   **Boudousquie C**, Bossi G, Hurst JM, Rygiel KA, Jakobsen BK, Hassan NJ. Polyfunctional response by ImmTAC (IMCgp100) redirected CD8(+) and CD4(+) T cells. *Immunology* 2017; **152**: 425-438 [PMID: 28640942 DOI: 10.1111/imm.12779]

59   **Middleton MR**, McAlpine C, Woodcock VK, Corrie P, Infante JR, Steven NM, Evans TRJ, Anthoney A, Shoushtari AN, Hamid O, Gupta A, Vardeu A, Leach E, Naidoo R, Stanhope S, Lewis S, Hurst J, O'Kelly I, Sznol M. Tebentafusp, A TCR/Anti-CD3 Bispecific Fusion Protein Targeting gp100, Potently Activated Antitumor Immune Responses in Patients with Metastatic Melanoma. *Clin Cancer Res* 2020; **26**: 5869-5878 [PMID: 32816891 DOI: 10.1158/1078-0432.CCR-20-1247]

60   **Harper J**, Adams KJ, Bossi G, Wright DE, Stacey AR, Bedke N, Martinez-Hague R, Blat D, Humbert L, Buchanan H, Le Provost GS, Donnellan Z, Carreira RJ, Paston SJ, Weigand LU, Canestraro M, Sanderson JP, Botta Gordon-Smith S, Lowe KL, Rygiel KA, Powlesland AS, Vuidepot A, Hassan NJ, Cameron BJ, Jakobsen BK, Dukes J. An approved in vitro approach to preclinical safety and efficacy evaluation of engineered T cell receptor anti-CD3 bispecific (ImmTAC) molecules. *PLoS One* 2018; **13**: e0205491 [PMID: 30321203 DOI: 10.1371/journal.pone.0205491]

61   **Chen LN**, Carvajal RD. Tebentafusp for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. *Expert Rev Anticancer Ther* 2022; **22**: 1017-1027 [PMID: 36102132 DOI: 10.1080/14737140.2022.2124971]

62   **Carvajal RD**, Butler MO, Shoushtari AN, Hassel JC, Ikeguchi A, Hernandez-Aya L, Nathan P, Hamid O, Piulats JM, Rioth M, Johnson DB, Luke JJ, Espinosa E, Leyvraz S, Collins L, Goodall HM, Ranade K, Holland C, Abdullah SE, Sacco JJ, Sato T. Clinical and molecular response to tebentafusp in previously treated patients with metastatic uveal melanoma: a phase 2 trial. *Nat Med* 2022; **28**: 2364-2373 [PMID: 36229663 DOI: 10.1038/s41591-022-02015-7]

Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: https://www.f6publishing.com/helpdesk

https://www.wjgnet.com