## ABOUT THE AUTHOR

**Cynthia Fournier, MD, FRCPC**

Dr. Cynthia Fournier is a board-certified dermatologist in Canada since 2022. She obtained her medical degree and completed her dermatology residency at Laval University. She then completed a fellowship in cutaneous oncology at the University of Toronto and she graduated in 2023. She trained at Princess Margaret Cancer Center. She has expertise and interest in the management of skin cancer and dermatological toxicities of cancer treatments such as immunotherapy, chemotherapy, and targeted therapy. She will start her academic practice at the Hôtel-Dieu-de-Lévis affiliated to the Laval University in 2023.

**Affiliations:** Hôtel-Dieu-de-Lévis, Lévis, QC

# TEBENTAFUSP: A NEW SYSTEMIC TREATMENT FOR UNRESECTABLE OR METASTATIC UVEAL MELANOMA IN HLA-A*02:01-POSITIVE PATIENTS

## Introduction

Uveal melanoma (UM) is the most common intraocular cancer in adults. It is distinct from cutaneous melanoma in terms of its mutations, metastatic pattern and treatment response. UM commonly metastasizes to the liver. Tebentafusp is a new systemic treatment approved for unresectable or metastatic UM in HLA-A*02:01-positive adult patients.[1] Tebentafusp is a bispecific protein consisting of an affinity-enhanced T-cell receptor fused to an anti-CD3 effector that can redirect T cells to target glycoprotein 100 (gp100) positive cells.[1] Tebentafusp is administered intravenously weekly. For UM, it is superior to immune checkpoint inhibitors with superior overall survival (OS) and progression-free-survival (PFS).[1] Tebentafusp commonly induces dermatological toxicities.

## Uveal Melanoma

Between 3.7% and 5% of melanomas occur in the eye.[2,3] Ocular melanomas originate from melanocytes situated in various parts of the eye and are subdivided into UM, conjunctival melanoma (CM), orbital melanoma, and eyelid melanoma. The vast majority of ocular melanomas are primary; however, they can also represent an ocular metastasis from a distant cutaneous melanoma. UM is the most common primary ocular melanoma subtype, with an 83% incidence; in addition, it is the most common primary intraocular malignancy in adults.[3] UM originates from melanocytes within the choroidal plexus (90%), the ciliary body (6%), or the iris (4%).[4] UM is distinct from its cutaneous counterpart in terms of genetic mutations, metastatic spread, tumour-immune microenvironment, and response to treatment. UM is distinct from conjunctival melanoma. CMs share more similarities with cutaneous melanoma than with UM.

The mean age at diagnosis for UM is 58-years-old.[5] Risk factors include older age; Caucasian population; fair skin colour; inability to tan; propensity to sunburn; light eye colour; oculodermal melanocytosis (nevus of Ota); atypical cutaneous nevi; cutaneous freckles; and uveal nevus.[4-6] The role of solar UV exposure in

the development of UM is uncertain; the clinical data is inconclusive.[5] Artificial UV exposure from welding is a well-known risk factor for UM.[5] Patients with BAP1 tumour predisposition syndrome are at higher risk of UM, in addition to cutaneous melanomas, basal cell carcinoma (BCC), malignant mesothelioma, and renal cell carcinoma (RCC).[4] Patients with xeroderma pigmentosum (XP) are also at increased risk of ocular melanoma, including melanoma originating from the iris and the choroid.[7]

UM lacks typical cutaneous melanoma mutations (BRAF, NRAS, KIT) but commonly harbors GNAQ and GNA11 mutations,[8,9] such as benign blue nevi and malignant blue nevi. Mutations in GNAQ or GNA11 result in constitutive activation of the MAPK pathway. Inactivating somatic mutations in BAP1 and decrease or complete loss of PTEN have also been found in UM.[5] The BAP1 and SF3B1 mutations are associated with a higher risk of metastatic spread.[5]

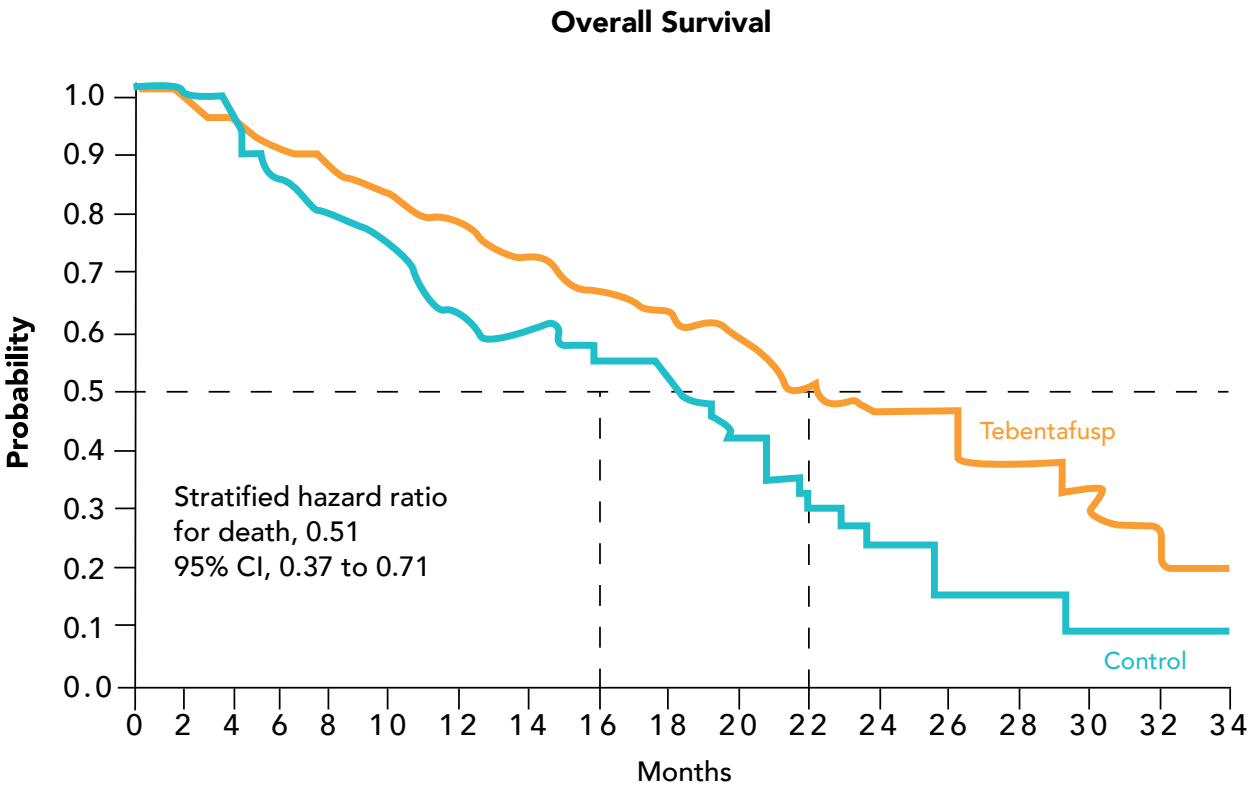
Fewer than 4% of patients have detectable metastatic disease at the time of diagnosis; however, approximately 50% of patients with UM will develop metastases.[5] Poor prognostic factors for metastatic risk include increasing age; larger tumour diameter; greater tumour thickness; UM arising from the ciliary body; loss of chromosome 3 in the tumour; mutations in the *BAP1* and *SF3B1* gene; and UM in a patient with BAP1 tumour predisposition syndrome.[5] In addition, posterior UM has a worse prognosis vs the anterior type. Patients with high-risk UM need regular follow-up for the early detection of metastases, with a liver MRI every six months and chest x-rays or a chest CT scan every 12 months.

UM disseminates hematogenously and has a very strong propensity to metastasize to the liver.[5] Ninety-three percent of patients with metastatic UM have disease in the liver, followed by 24% in the lungs and 16% in the bones.[10] UM can also spread to the brain and the skin.[5] UM typically does not metastasize to the lymph nodes due to a lack of lymphatic spread, except when UM perforates the sclera and infiltrates the conjunctival lymphatics; however, this rarely occurs.[5] Metastatic spread confers a very poor prognosis with a median overall survival (mOS) of 10.2 months.[11] UM is a deadly cancer. In a cohort of 289 patients with UM, UM-related mortality was 31% by five years, 45% by 15 years, 49% by 25 years, and 52% by 35 years.[12]

Local treatments for primary uveal malignant tumours include transpupillary thermotherapy; photodynamic therapy; plaque brachytherapy; proton beam radiotherapy; local resection; and enucleation.[4] Most patients are treated with plaque brachytherapy or enucleation. Systemic treatments for metastatic UM include tebentafusp, immunotherapy and conventional chemotherapy.[13] Immunotherapy has revolutionized the treatment of many cancers including Stages III and IV cutaneous melanoma, with significant survival benefit. However, response to immunotherapy in metastatic UM is disappointing, due to a different tumour-immune microenvironment and UM low tumour mutational burden. Survival is not increased with the use of single-agent ipilimumab, nivolumab or pembrolizumab.[13] Combination immunotherapy using ipilimumab plus nivolumab benefits patients with metastatic UM, with increased overall survival up to 18–19 months; however, this double immunotherapy is significantly more toxic than the single-agent form, with frequent Grade 3 and Grade 4 immune-related adverse events.[13] Stage IV UM, like cutaneous melanoma, tends to be chemo-resistant. Dacarbazine, fotemustine and temozolomide can be used, but represent a last option. Metastases can also benefit from local treatments using surgical excision, intra-arterial liver chemotherapy, hepatic arterial chemoembolization, liver radioembolization, and stereotactic radiosurgery.[13]

## Tebentafusp Mechanism of Action, Indications and Dosing

Tebentafusp has been Health Canada and United States Food and Drug Administration (FDA)-approved since 2022 for HLA-A*02:01-positive adult patients with unresectable or metastatic UM. Forty-five percent of individuals in the United States and Europe are HLA-A*02:01-positive and HLA testing is conducted via serology prior to initiating tebentafusp.[1] For UM, tebentafusp is superior to immune checkpoint inhibitors (ICIs) and chemotherapy with superior OS and PFS. A recent Phase 3 trial compared patients receiving tebentafusp to patients receiving the investigator's choice of treatment with single-agent pembrolizumab, ipilimumab or dacarbazine.[1] The estimated OS at one year was 73% (95% confidence interval [CI], 66–79) in the tebentafusp group and 59% (95% CI, 48–67) in the control group (**Figure 1**). There was a survival benefit in patients with cancer progression receiving tebentafusp vs patients with cancer progression in the control group. The estimated PFS at six months was 31% in the tebentafusp group vs 19% in the control group (stratified hazard ratio for disease progression or death, 0.73; 95% CI, 0.58–0.94; P=0.01). Forty-six percent (95% CI, 39–52) of patients receiving tebentafusp had disease control (complete response,




| 1-Year Survival | | |
|---|---|---|
| Tebentafusp Group | 73% | 95% CI, 66 to 79 |
| Control Group | 59% | 95% CI, 48 to 67 |

***Figure 1.*** *Estimated 1-year survival in tebentafusp group vs control group; adapted from Nathan, P et al, 2021.*

partial response or stable disease for ≥12 weeks) vs 27% (95% CI, 20-36) in the control group.

Tebentafusp is a bispecific protein comprised of a soluble T-cell receptor fused to an anti-CD3 single-chain variable fragment-activating domain.[1] The high-affinity, high-specificity T-cell receptor targets a nine-amino-acid peptide derived from proteasomal degradation of the intracellular gp100 protein, presented by HLA-A*02:01 molecules on the surface of target cells, including skin melanocytes and tumours derived from melanocytes (UM). The anti-CD3 domain engages and activates CD3+ cells. By targeting a specific shared tumour-associated antigen, these T-cell receptor bispecific molecules can recruit T cells to target tumours independent of the presence of tumour antigen-specific T cells or of the tumour mutational status.[1] In summary, tebentafusp redirects the immune system to target and kill gp100-expressing UM tumour cells.

Tebentafusp is an intravenous infusion administered weekly. Doses are escalated over the first three weeks to reduce toxic effects: 20 µg on Day 1, 30 µg on Day 8, 68 µg on Day 15, and 68 µg weekly thereafter. Patients are admitted to hospital for overnight monitoring following their first infusions. Following several weeks of treatment, if treatment is well-tolerated, patients are transitioned to weekly infusions administered in an outpatient setting.

Since its approval tebentafusp has been used as a first-line treatment for HLA-A*02:01-positive patients with unresectable or metastatic UM. In patients who are HLA-A*02:01-negative, combination immunotherapy using ipilimumab and nivolumab remains the treatment of choice. If patients progress on tebentafusp, the typical subsequent treatment phase is the use of combined ipilimumab and nivolumab. As discussed previously, conventional chemotherapy remains a last option as melanomas are refractory to chemotherapy.

## Tebentafusp-related Adverse Events

Tebentafusp-related adverse events are subdivided into two main categories: cytokine-mediated and skin-related adverse events. In the majority of patients, toxicities occur in the initial four weeks of treatment during inpatient dose escalation. The incidence and severity of acute adverse events decrease with repeated dosing. Only 2% of patients permanently discontinue tebentafusp due to treatment-related adverse events.[1]

Many patients develop cytokine-mediated adverse events in the initial weeks of treatment; 76% have pyrexia, 47% experience chills and 38% have hypotension (**Table 1**).[1] A cytokine release syndrome, described by the combination of pyrexia, hypotension and hypoxia, commonly occurs within a few hours following the initial three infusions of tebentafusp. Patients are treated with antipyretics, intravenous fluids and systemic steroids.

Regarding dermatological adverse events, 69% of patients receiving tebentafusp experience pruritus and 83% of patients develop a "rash",[1,14,15] likely due to cytotoxic T cells attacking gp100-expressing normal melanocytes.[15] Patients typically develop the characteristic eruption in the initial four weeks of treatment in association with tebentafusp dose escalation. The eruption is clinically morbilliform to erythrodermic. Some patients develop impetigo-like superficial bullae and superficial erosions.[15] Two patients with a photo-distributed eruption were also described with erythema and edema in sun-exposed areas (face, neck, ears and dorsum of the hands) following the fourth treatment cycle.[17] The typical acute eruption and pruritus occur in the initial 24 hours following the infusion, last for 24–72 hours following each infusion, and lead to superficial exfoliative desquamation in the following week. Superficial desquamation can involve sites of resolving inflammation, as well as previously uninvolved skin. The eruption tends to increase in severity following each dose up to the second to forth infusions. After the third infusion, tebentafusp doses remain stable and the acute skin toxicities diminish in incidence and severity following each subsequent infusion, possibly due to gp100-expressing normal melanocytes being destroyed. Acute cutaneous adverse events eventually cease beyond the first three to six infusions. The early cutaneous eruption is associated with longer survival.[14,15]

The treatment of tebentafusp-associated acute skin toxicities is symptomatic. Pruritus is managed with cold compresses, oral or intravenous first-generation antihistamines (diphenhydramine), and oral second-generation antihistamines. Typical eruptions are managed using emollients, topical steroids and topical steroid wet wraps.

Tebentafusp is a new treatment and there is no guideline for the treatment of acute cutaneous adverse events. Treatment interruption is typically not indicated for cutaneous toxicities. The expert opinion is that treatment interruption may lead to a recurrence of the same skin toxicity with a similar severity when tebentafusp is re-introduced.

Fifty-seven percent of patients also develop late dermatological adverse events occurring after a median of 2.7 months: vitiligo-like hypopigmentation and depigmentation, hyperpigmentation, and leukotrichia.[14,18] Patients who experienced late pigmentary adverse events have 72% lower odds of mortality vs those who did not.[18]

## Conclusion

Tebentafusp is approved for unresectable or metastatic UM and acts by redirecting T cells to target gp100-positive cells. It commonly induces early (rash/pruritus) and late (pigmentary changes involving the skin and hair) cutaneous toxicities. Dermatologists have most likely been diagnosing and managing a greater number of tebentafusp-induced cutaneous toxicities since its approval by Health Canada and the FDA in 2022.

## Correspondence

**Dr. Cynthia Fournier**
**Email:** cynthia.fournier.2@ulaval.ca

## Financial Disclosures

**Consultant and/or Speaker:** Janssen, La Roche Posay, Sanofi, and Sun Pharmaceuticals

| Treatment-Related Adverse Events (Safety Population).* | | | | |
|---|---|---|---|---|
| **Event** | **Tebentafusp Group (N=245)** | | **Control Group (N=111)** | |
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| | *number of patients (percent)* | | | |
| Any treatment-related adverse event | 243 (99) | 109 (44) | 91 (82) | 19 (17) |
| Cytokine release syndrome» | 217 (89) | 2(1) | 3 (3) | 0 |
| Rash« | 203 (83) | 45 (18) | 27 (24) | 0 |
| Pyrexia | 185 (76) | 9 (4) | 3 (3) | 0 |
| Pruritus | 169 (69) | 11 (4) | 23 (21) | 0 |
| Chills | 114 (47) | 1 (<1) | 3 (3) | 0 |
| Nausea | 105 (43) | 2 (1) | 21 (19) | 0 |
| Fatigue | 101 (41) | 7 (3) | 29 (26) | 1 (1) |
| Hypotension | 93 (38) | 8 (3) | 0 | 0 |
| Dry Skin | 72 (29) | 0 | 4 (4) | 0 |
| Vomiting | 64 (26) | 1 (<1) | 7 (6) | 0 |
| Erythema | 56 (23) | 0 | 1 (1) | 0 |
| Headache | 53 (22) | 1 (<1) | 3 (3) | 1 (1) |
| Aspatate aminotransferase increased | 47 (19) | 11 (4) | 9 (8) | 0 |
| Alanine aminotransferase increased | 43 (18) | 7 (3) | 8 (7) | 2 (2) |
| Lipase increased | 32 (13) | 9 (4) | 7 (6) | 6 (5) |
| Diarrhea | 31 (13) | 2 (1) | 16 (14) | 3 (3) |
| Lymphopenia | 22 (9) | 6 (2) | 2 (2) | 0 |
| Hyperbilirubinemia | 21 (9) | 5 (2) | 2 (2) | 0 |
| Hypophosphatemia | 19 (8) | 7 (3) | 1 (1) | 0 |
| Hypertension | 15 (6) | 9 (4) | 2 (2) | 1 (1) |

***Table 1.*** *Treatment-Related Adverse Events (Saftey Population); courtesy of Dr. Cynthia Fournier.*

* Shown are treatment-related adverse events that were reported in at least 20% of patients (any grade) or in at least 2% of patients (grade >3) in either group.

» Cytokine release syndrome was graded according to the 2019 recommendations of the Americain Society for Transplantation and Cellular Therapy for consensus grading for cytokine release syndrome.[21]

» Rash is a composite term for a list of skin-related adverse events of any grade.

## References


1. Nathan P, Hassel JC, Rutkowski P, et al. Overall survival benefit with tebentafusp in metastatic uveal melanoma. New England Journal of Medicine. 2021;385(13):1196-1206.
2. McLaughlin CC, Wu XC, Jemal A, Martin HJ, Roche LM, Chen VW. Incidence of noncutaneous melanomas in the U.S. Cancer. 2005;103(5):1000-1007.
3. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer. 1998 Oct 15;83(8):1664-78.
4. Kaliki S, Shields CL. Uveal melanoma: relatively rare but deadly cancer. Eye. 2016;31(2):241-257.
5. Jovanovic P, Mihajlovic M, Djordjevic-Jocic J, Vlajkovic S, Cekic S, Stefanovic V. Ocular melanoma: an overview of the current status. Int J Clin Exp Pathol. 2013 Jun 15;6(7):1230-44.
6. Nayman T, Bostan C, Logan P, Burnier MN. Uveal melanoma risk factors: a systematic review of meta-analyses. Current eye research. 2017;42(8):1085-1093.
7. Vivian AJ, Ellison DW, McGill JI. Ocular melanomas in xeroderma pigmentosum. British Journal of Ophthalmology. 1993;77(9):597-598.
8. Van Raamsdonk CD, Bezrookove V, Green G, et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. Nature. 2008;457(7229):599-602.
9. Van Raamsdonk CD, Griewank KG, Crosby MB, et al. Mutations in GNA11in uveal melanoma. New England Journal of Medicine. 2010;363(23):2191-2199.
10. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS). Archives of Ophthalmology. 2001;119(5):670.
11. Khoja L, Atenafu EG, Suciu S, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2019;30(8):1370-1380.
12. Kujala E, Ma¨kitie T, Kivela¨ T. Very long-term prognosis of patients with malignant uveal melanoma. Investigative Ophthalmology & Visual Science. 2003;44(11):4651.
13. Rodriguez-Vidal C, Fernandez-Diaz D, Fernandez-Marta B, et al. Treatment of metastatic uveal melanoma: systematic review. Cancers. 2020;12(9):2557.
14. Hassel JC, Rutkowski P, Baurain J-F, Butler MO, Schlaak M, Sullivan R, et al. Co-primary endpoint of overall survival for tebentafusp (tebe)-induced rash in a phase 3 randomized trial comparing tebe versus investigator's choice (IC) in first-line metastatic uveal melanoma. J Clin Oncol. 2021; 39: 9527.
15. Middleton MR, McAlpine C, Woodcock VK, Corrie P, Infante JR, Steven NM, et al. 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(22):5869-78.
16. Pham J, Star P, Ardolino L, Smith A, Joshua AM. A review of the cutaneous toxicities of tebentafusp—featuring two cases involving superficial bullous reactions. Australas J Dermatol. 2022;63(3).
17. Lambertini M, Comito F, Melotti B, Baracca MF, Dika E. Drug-induced photosensitivity during tebentafusp treatment for metastatic uveal melanoma: A newly described occurrence. Journal of the European Academy of Dermatology and Venereology. 2022;37(2):e207-e208.
18. Orloff M, Sacco JJ, Nathan PC, et al. Abstract 3295: Vitiligo and other clinical melanocyte-related adverse events following tebentafusp (IMCgp100) exposure in patients with uveal melanoma. Cancer Research. 2020;80.