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Escape From Synthetic T Cell Activator Tebentafusp by Genomic HLA Loss: A Case Report

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ABSTRACT

Tebentafusp, a T-cell receptor-bispecific molecule targeting glycoprotein 100-derived peptide presented by HLA class I molecule and CD3, is standard of care for patients with unresectable or metastatic uveal melanoma who are positive for *HLA-A*02:01*. Mechanisms of resistance to tebentafusp are unknown. We report a patient with metastatic uveal melanoma who acquired resistance to tebentafusp after 30 months of treatment. Genomic loss of the HLA-haplotype carrying the *HLA-A*02:01* restriction element was detected in a progressive metastasis, resulting in loss of presentation of tebentafusp's target antigen. Understanding mechanisms of resistance against synthetic cancer immunotherapies will be key to monitoring disease control and development of early intervention strategies towards cure.

1 | Introduction

Immunotherapies have become an important pillar in cancer treatment. Beyond immune checkpoint blockade (ICB) with antibodies targeting immune regulatory surface proteins PD-1, PD-L1, CTLA-4 and LAG-3, synthetic biomolecules that redirect T cells to cancer cells by targeting tumour antigens emerged as a new class of agents. This strategy is further extended to intracellular tumour antigens presented by cancer cells through HLA class I molecules. As such the bispecific antibody tebentafusp activates T cells against glycoprotein 100 (gp100)-derived peptide presented by HLA class I molecule *HLA-A*02:01*, which is expressed by approximately 40% of the Western Europeans [1]. gp100 (also known as PMEL17) is a melanocyte lineage-specific melanosomal structural protein expressed in normal melanocytes and melanoma cells [2]. Hence, therapeutic side effects of tebentafusp are not limited to cytokine release syndrome but mostly include dermatological adverse events like rush and pruritus [3].

Tebentafusp is the first ever treatment demonstrating a survival benefit in patients with metastatic uveal melanoma (UM) [4], a rare cancer entity with aggressive behaviour and inevitably fatal outcome once it has metastasised [5–7]. Nearly every second

patient with primary UM develops metastases, mostly to the liver. The median duration of response towards tebentafusp is 11.1 months [8]. Importantly, UM displays a distinct immunobiology compared to other solid tumours, which has implications for response and resistance to immunotherapy including a divergent pattern of HLA regulation [9–11]. For instance, primary UM lesions typically exhibit low inflammatory infiltration consistent with low tumour mutational burden as well as limited T cell infiltration and variable to low HLA class I expression in the context of ocular immune privilege [11]. Notably, metastatic lesions, particularly in the liver, are often associated with increased inflammatory signalling and upregulation of HLA expression [6, 7, 10]. Recent transcriptomic analyses of tumours from patients treated with Tebentafusp further indicate that expression of the antigen presentation machinery is associated with the clinical outcome [12]. Nevertheless, selective loss of individual HLA alleles or haplotypes might serve as a mechanism to evade T cell recognition while preserving sufficient HLA expression to avoid natural killer cell-mediated clearance in some cancers [13, 14]. In UM, such allele-specific alterations remain incompletely characterised, and their role in metastatic dissemination and resistance to antigen-specific therapies such as tebentafusp is largely unexplored.

Herein, we are the first to establish genomic loss of the relevant *HLA-A*02:01* restriction element as a mechanism of acquired resistance in liver metastases of a patient with UM, which progressed after 30 months of treatment with tebentafusp.

2 | Case Report

A 69-year-old man was diagnosed with uveal melanoma of the right eye in 2021, which was treated by local brachytherapy using a ruthenium applicator. Genetic workup of the primary tumour revealed *GNAQ* (encoding for guanine nucleotide-binding protein G(q) subunit alpha) and *BAP1* (encoding for BRCA1-associated protein 1) mutations. Only 4 months after primary diagnosis, liver metastases were detected by magnet resonance imaging (MRI) (Figure 1A). Initial treatment included the resection of two metastases in liver segments 2 and 3. However, rapid disease progression presenting with new bilobar liver metastases required systemic therapy. The patient was enrolled in a clinical trial to receive 4 cycles of a vaccine based on autologous dendritic cells primed with tumour RNA and peptides, along with the immune checkpoint blocking antibodies pembrolizumab and ipilimumab (NCT04335890). Nevertheless, progressive liver metastases were demonstrated within 4 months from first vaccination. Next, one course of selective intraarterial radiotherapy (SIRT) was applied only to the right liver. Given that the patient was positive for *HLA-A*02:01*, in 2022, he was enrolled in an early access programme with tebentafusp, which—after updosing—was administered at weekly intravenous doses of 68 μg from 2022 to 2024. Radiologically confirmed best response of his liver metastases was partial remission per Response Evaluation Criteria in Solid Tumours (RECIST). Overall, treatment was well tolerated, with only mild cutaneous adverse events, including grade II pruritus and grade I rash occurring the day after infusion and remaining stable throughout the treatment period with tebentafusp. In October 2024, progressive liver metastases and new hepatic lesions were documented by MRI (Figure 1B), associated with increased levels of liver enzymes and LDH. Acquired resistance was diagnosed, and the patient provided written informed consent for a CT-guided biopsy of a progressive liver lesion in segment 4 for diagnostic workup and exploration of resistance mechanisms.

3 | Methods

3.1 | Immunohistochemistry

Formalin-fixed paraffin-embedded (FFPE) sections from hepatic metastases resected before any systemic therapy and liver biopsy taken from progressive metastases, which were present before tebentafusp therapy, were processed for immunohistochemistry. Following deparaffinisation, heat-induced epitope retrieval was performed using citrate buffer (pH 6) or Tris/EDTA buffer (pH 9). Slides were blocked with serum-free protein blocking solution (Zytomed, ZUC007-100), and incubated overnight at 4°C either with anti-CD8 (Abcam, ab101500, 1:200), anti-CD45 (Abcam, ab10558, 1:400), or anti-Melan-A (Proteintech, 18472-1-AP, 1:750). Secondary antibody (Zytomed, ZUC053) was applied for 30 min at room temperature, followed by DAB chromogen development (Dako, K3468). Finally, slides were counterstained with haematoxylin, dehydrated, and mounted. Slides were scanned by Zeiss Axio Scanner Z.1 (Carl Zeiss AG, Germany), with a 10× objective magnification.

3.2 | HLA Genotyping

Dark pigmented tissue was macrodissected from the liver biopsy taken at progression under tebentafusp. Metastasis DNA was isolated with DNeasy Blood and Tissue Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions. Germ line DNA from peripheral blood (PB) was isolated using the chemagic Prime kit (chemagen Technologie GmbH, Baesweiler, Germany). Full-gene 2nd field next-generation-sequencing (NGS) of the HLA-A, -B and -DRB1 loci was performed on the Illumina iSeq100 platform using the NGSgo AmpX v2 kit (GenDx, Utrecht, Netherlands) per manufacturers' instructions. The number of reads for both alleles of each locus in metastasis-derived DNA and germ line DNA were called and compared using the NGSengine software version 3.1.2 (GenDx, Utrecht, the Netherlands).

4 | Results

Immunohistochemical analyses of hepatic metastases resected before any systemic therapy and liver biopsy taken after progression upon tebentafusp-therapy, showed no difference in infiltrates of CD45+ and CD8+ T cells, which was low in both tumour samples (Figure 1C). Germline HLA typing of PB revealed the presence of 3 possible HLA-A, -B, -DRB1 heterozygous haplotypes, with haplotype combination A and B most frequent in Western populations [15], and haplotype B carrying *HLA-A*02:01* (Table 1). As expected, the NGS read numbers for both haplotypes were similar in germline DNA (mean 49.1% ± 5.3% and 47.5% ± 2.2% for haplotype A and B, respectively; Figure 2 and Table 2). In contrast, a marked imbalance

in favour of haplotype A (mean 76.6% ± 2.5%) over haplotype B (mean 23.4% ± 2.5%) was revealed in metastasis-derived DNA (Figure 2 and Table 2). These findings are compatible with loss of heterozygosity (LOH) by deletion of haplotype B, carrying *HLA-A*02:01* target of the tebentafusp immunotherapy in the treatment-resistant metastasis. The remaining reads for

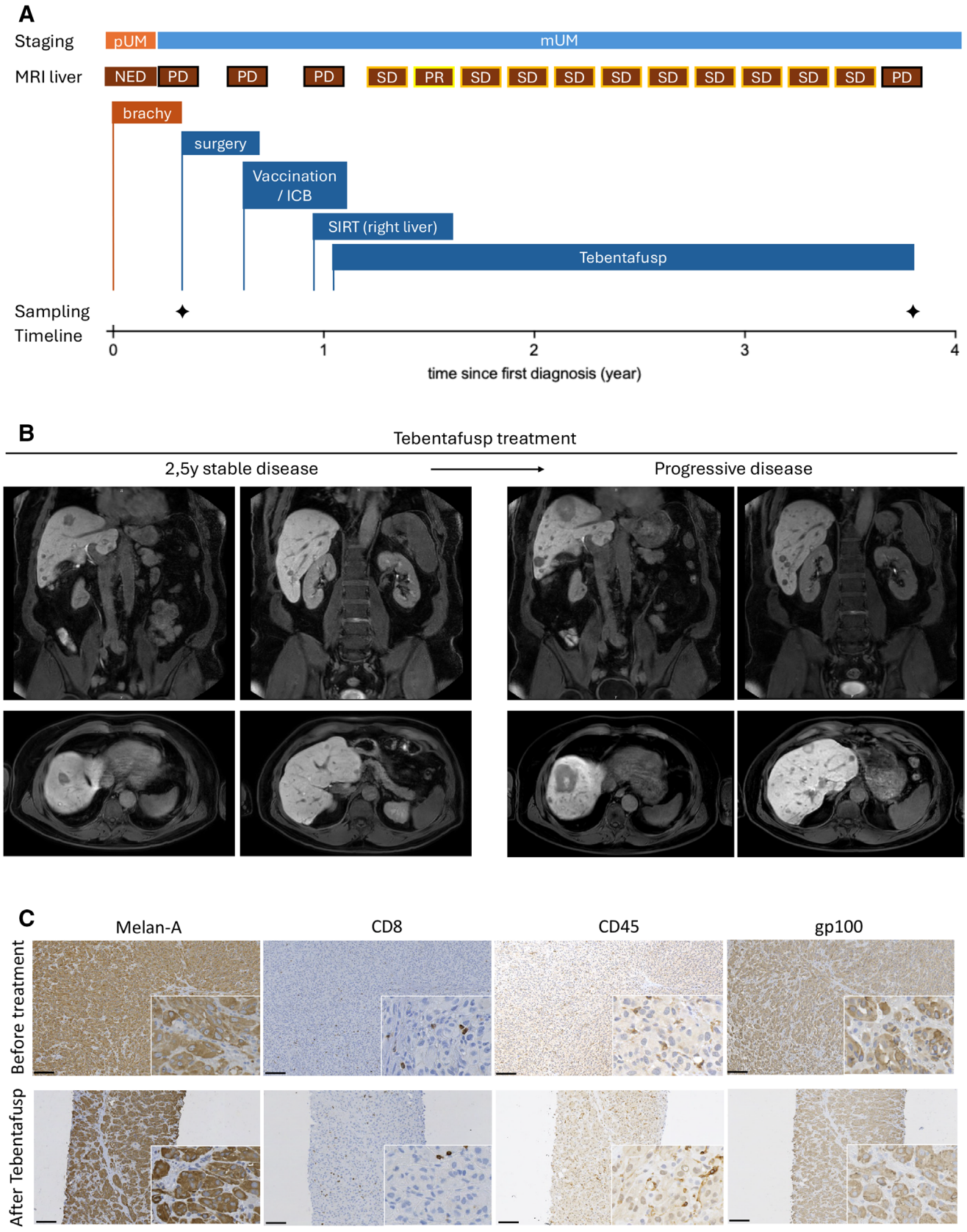

FIGURE 1 | Legend on next page.

FIGURE 1 | Patient history of clinical benefit and acquired resistance to tebentafusp. (A) Graphic representation of disease, treatment history and tumour sample collection (✦). During tebentafusp treatment disease control in the liver was monitored by MRI scans every 3 months (pUM, primary uveal melanoma; mUM, metastatic uveal melanoma; NED, no evidence of disease; PD, progressive disease; PR, partial remission; SD, stable disease; brachy, brachytherapy of the ocular tumour; ICB, immune checkpoint blocking antibody therapy; SIRT, selective intraarterial radiotherapy). (B) Representative MRI scans demonstrating stable (left panel) and progressive (right panel) liver metastases. Sagittal (top) and transversal (bottom) images are shown. (C) Immunohistochemistry of liver metastasis before any systemic treatment (from resection) and after treatment with tebentafusp (from biopsy) demonstrating Melan A, CD8, CD45 and gp100 staining of tumour tissue.

TABLE 1 | Possible HLA-A, -B and -DRB1 haplotypes in the patient.

Haplotype number	HLA-A	HLA-B	HLA-DRB1	Haplotype frequency	Probability haplotype combination
A	*01:01	*08:01	*03:01	7.404	59%
B	*02:01	*55:01	*04:01	0.004	
C	*01:01	*55:01	*04:01	0.019	34%
D	*02:01	*08:01	*03:01	0.896	
E	*01:01	*08:01	*04:01	0.235	7%
F	*02:01	*55:01	*03:01	0.015	

Note: Second-field HLA-A, -B and -DRB1 typing was performed on the patient's blood-derived germline DNA. Haplotype assignment was performed based on reported HLA haplotype frequencies for European Americans (white, or Caucasian) [16].

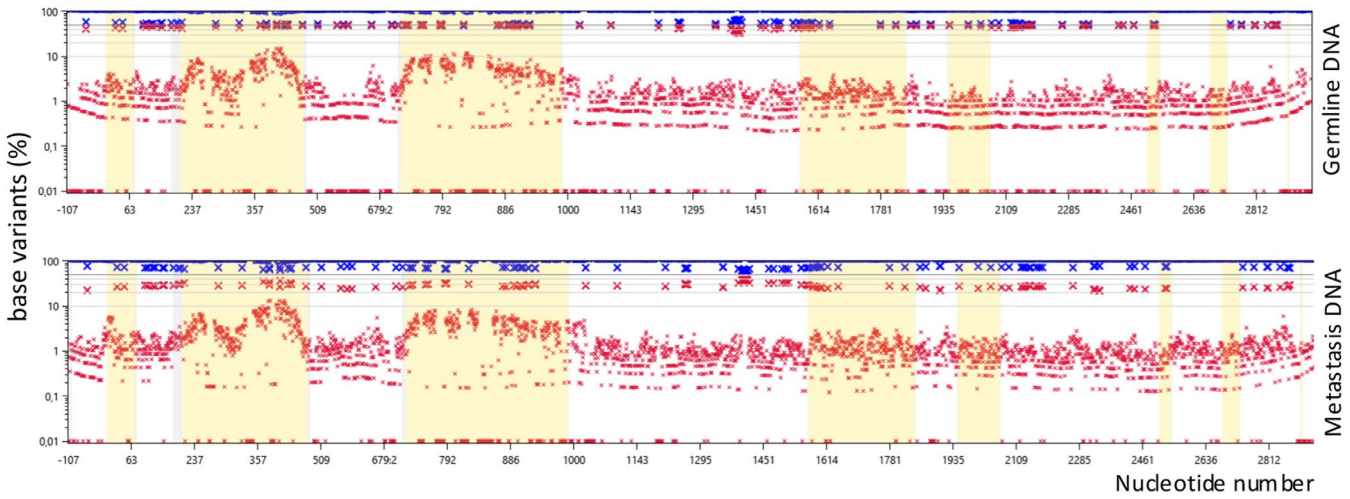

FIGURE 2 | Genomic loss of an entire HLA haplotype in the tumour metastasis. Second-field NGS-based HLA-A typing of blood-derived germline DNA (upper panel) or liver biopsy-derived metastasis DNA (lower panel). Shown is the percentage of base variants over the full-length HLA-A gene (positions −100 to +2820). Heterozygous positions are signed on top by a bold upper-case X, either to the HLA-A allele with the higher average base variant percentage (blue) or to the HLA-A allele with the lower average base variant percentage (red). Unassigned base variants (background) are marked below with a lower-case red x. Note that the average base variant percentage for *HLA-A*01:01* and *HLA-A*02:01* are superimposable in the germline DNA (bold red and blue X), while there is a marked difference between the average base variant percentage for *HLA-A*01:01* (bold blue X) and *HLA-A*02:01* (bold red X) in the metastasis DNA. Similar results were obtained also for the two other HLA loci, with lower average base percentages for *HLA-B*55:01* compared to *HLA-B*08:01*, and *DRB1*04:01* compared to *HLA-DRB1*03:01* (not shown).

haplotype B in the biopsy are likely from contaminating normal liver tissue, although the possibility that LOH did not occur in all tumour cells in the biopsy cannot be ruled out.

5 | Discussion

Tebentafusp is the first systemic therapy to ever demonstrate an overall survival benefit in patients with metastatic UM. Compared to non-specific immunotherapy using ICB antibodies, which have limited activity in UM [6], tebentafusp acts in an antigen-specific manner: establishing a synthetic immunological synapse between cancer cells presenting gp100-derived antigen in *HLA-A*02:01* context, and T cells activated by engagement of the CD3 surface protein [5]. This mode of action is expected to therapeutically direct effector T cells to gp100-derived peptide expressing UM cells without the requirement of endogenous gp100-derived peptide avid T cell receptors,

TABLE 2 | Read percentage for each of the two HLA-A, -B and -DRB1 alleles in the germline or metastasis DNA.

	Haplotype number	Allele	%reads	Allele	%reads	Allele	%reads
Germ line	A	A*01:01	49.8	B*08:01	55.3	DRB1*03:01	52.4
	B	A*02:01	50.2	B*55:01	44.7	DRB1*04:01	47.6
Metastasis	A	A*01:01	74.9	B*08:01	74.7	DRB1*03:01	80.2
	B	A*02:01	25.1	B*55:01	25.3	DRB1*04:01	19.8

Note: The imbalance between the read percentages in the metastasis DNA demonstrates loss of heterozygosity by deletion of haplotype B, encompassing *HLA-A*02:01*, in at least a part of the tumour cells. The average read depth in exons 2 and 3 for HLA-A, -B and -DRB1 of the germline DNA was 343, 329 and 412, respectively. The average read depth in exons 2 and 3 for HLA-A, -B and -DRB1 of the metastasis DNA was 610, 519 and 483, respectively.

which may be depleted in patients by tolerance mechanisms. Despite its confirmed clinical efficacy, the majority of *HLA-A*02:01*-positive patients with metastatic UM do not respond or ultimately acquire resistance to tebentafusp [8]. Understanding mechanisms of tebentafusp-resistance may have broader implications for novel antigen-specific synthetic cancer immunotherapies. Here, we are the first to report somatic genomic loss of the relevant *HLA-A*02:01* restriction element, essential for targeting gp100-derived peptide expressing cancer cells by tebentafusp, as clinically relevant tumour escape mechanism. Interestingly, the molecular mechanism leading to the genomic HLA loss was not a targeted deletion of the allele by itself, but encompassed the entire HLA-A, -B, DRB1 haplotype. Frequently, this is accompanied by duplication of the remaining haplotype (uniparental disomy, UPD), resulting in an overall unaltered copy number variation of HLA class I molecules expressed by the cancer cells, thereby circumventing attack from natural killer cells recognising missing HLA. This mechanism has been shown to occur in leukaemia relapses after HLA-mismatched haematopoietic cell transplantation, with UPD specifically targeting the entire haplotype carrying the mismatched HLA [15, 17, 18]. Moreover, genomic or transcriptional loss of HLA class I, and of parts of the HLA class I peptide processing machinery, have been described in immune escape mechanisms also for solid tumours [13, 14, 19, 20]. In line, transcriptomic analyses of tumours from Tebentafusp-treated patients indicate that the expression of the antigen presentation machinery is associated with overall survival [12]. Although longitudinal sampling was not feasible to determine the exact timing of LOH, the sustained initial clinical response to *HLA-A*02:01*-restricted therapy strongly suggests the presence of *HLA-A*02:01* at treatment initiation. Interestingly, the durable initial clinical response to Tebentafusp occurred despite the low $CD8^+$ T-cell infiltration observed in the liver biopsy obtained at progression. This finding may reflect the distinct mechanism of action of tebentafusp, which redirects circulating polyclonal T cells towards gp100-derived peptide-presenting tumour cells and may therefore not require high baseline intratumoral T-cell infiltration. In addition, the analysed biopsy was obtained after prolonged treatment and at the time of acquired resistance, potentially representing an evolved immune escape phenotype, which might be distinct from the immune microenvironment at treatment initiation.

Our study demonstrates that HLA can be central to the escape from adoptive cellular cancer therapy by tebentafusp-mediated T cell activation. It confirms the relevance of *HLA-A*02:01*-presented gp100-derived peptide as therapeutic tumour-antigen, and supports the potency of synthetic antigen-specific T cell activation by T cell-receptor fusion proteins as it similarly induces a "seek and hide" escape mechanism in a metastatic cancer. Further, our observation suggests that investigation of the specific mechanisms underlying disease recurrence is of practical importance. The resistance mechanism described herein rendered our patient unresponsive to all other *HLA-A*02:01*-dependent therapeutic immune interventions. Also, demonstration of strong imbalance of *HLA-A*02:01* expression in UM metastases may serve as a predictor of primary resistance to tebentafusp, a treatment with substantial burden for patients and the healthcare system.

Our findings encourage the clinical development of alternative gp100-derived peptide directed cancer immunotherapies [21], such as gp100-derived peptide targeted vaccinations (upon other epitopes included) which are in clinical development (NCT00003665, NCT00334776) [22, 23]. Combining tebentafusp with agents building on non-immunological mechanisms of action, such as the antibody-drug conjugate DYP688 (NCT05415072) targeting GNAQ11 and PMEL17, or the protein kinase C (PKC) inhibitor darovasertib (NCT05987332) may be another option to synergistically target metastatic UM to reduce the likelihood of success for a single escape and resistance mechanism.

Importantly, this clinical case undermines the importance of re-biopsies and characterisation of mode of resistance for future guidance of therapeutic choices, aiming to enable appropriate strategies of relapse treatment apt to circumvent specific resistance mechanisms and avoid exposing patients to cross-resistant treatments.

Author Contributions

Data collection: Halime Kalkavan, Andreas Heinold, Siyang Liu, Gaurav M. Borse, Falko M. Heinemann, Thomas Dertnig, Jörg Hense, Marc Ingenwerth, Fung-Yi Cheung, Georgia Antonopoulou, Ina Pretzell, Martin Schuler. Data interpretation: Halime Kalkavan, Andreas Heinold, Siyang Liu, Thomas Dertnig, Fung-Yi Cheung, Georgia Antonopoulou, Ina Pretzell, Katharina Fleischhauer, Nikolaos E. Bechrakis, Martin Schuler. Manuscript: Halime Kalkavan, Andreas Heinold, Katharina Fleischhauer, Nikolaos E. Bechrakis, Martin Schuler. Overall supervision: Halime Kalkavan, Martin Schuler.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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