Tebentafusp treatment slows disease progression in previously treated malignant uveal melanoma: A 20-Month Case Follow-up Report

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Introduction

Survival rates are low in patients with metastatic uveal melanoma, and no treatments have been proven to benefit survival. However, in the recent trial by Nathan P et al Tebentafusp has shown overall survival of 73% at 1 year vs 59% by the Investigator's Choice.

Ocular melanoma is the most common ocular, malignancy with five years metastasis incidence rate of 25% with liver being the most common site of metastasis (89%). [1] Metastasis is a poor prognostic factor with a median survival of less than a year. [1,2]

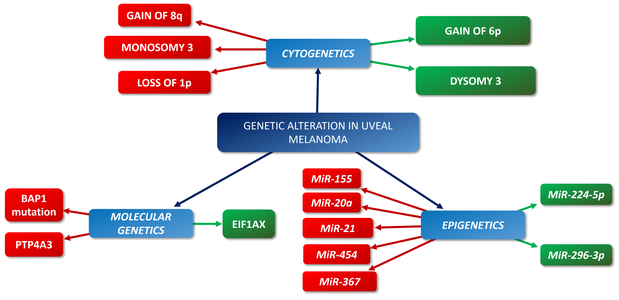
Risk Factors

a) Environmental: [4,5]

UV and Blue Spectrum light, light coloured eyes, fair skin, ocular melanocytosis, xeroderma pigmentosum, dysplastic nevus syndrome.

b) Genetic: [20]

- Chromosomal: (monosomy 3, disomy 3, gain of 8q, gain of 6p)
- Molecular: (**GNAQ**+GNA11, BAP, EIF1AX)
- Epigenetic: (Methylation, micro-RNA)



ure 1: Genetic Variations in Uveal Melanoma(Red= High risk of metastasis, Green= Low risk of metastasis)

Treatment Options

a) Immune checkpoint inhibitor

While immunotherapy alone using different agents (ipilimumab, pembrolizumab, or nivolumab) has shown limited results, the combination therapy (of ipilimumab with one of the previously mentioned agents) has offered encouraging results with an overall survival rate of around 19 months. [7]

b) Chemotherapy

Conventional chemotherapy agents as single agent and in combination have been ineffective (6).

c) *Tebentafusp*

Tebentafusp is a first-in-class bispecific fusion protein (ImmTAC® (Immune mobilizing monoclonal TCRs Against Cancer) designed to target gp100 (a melanoma-associated antigen) bound to HLA A0201 through a high affinity T-cell receptor (TCR) binding domain and an anti-CD3 T-cell engaging domain, which redirects T cells to kill gp100-expressing tumour cells. Data from the largest Phase 3 trial conducted by Nathan Pet al. undertaken in untreated metastatic malignant melanoma, showed that Tebentafusp demonstrated unprecedented median OS benefit as a first-line treatment.

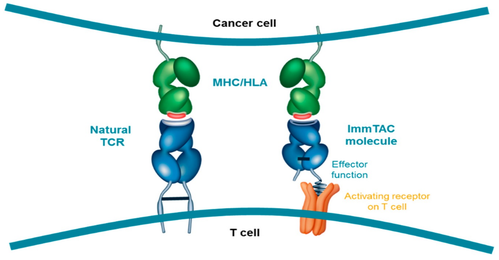


***Figure 2a**: Illustration of Tebentafusp Structure [9]*

The estimated overall survival at 1 year was 73% (95% confidence interval [CI], 66 to 79) in the tebentafusp group and 59% (95% CI, 48 to 67) in the control group; the estimated median duration of overall survival was 21.7 months (95% CI, 18.6 to 28.6) and 16.0 months (95% CI, 9.7 to 18.4), respectively. The stratified hazard ratio for death was 0.51 (95% CI, 0.37 to 0.71; P<0.001) in favour of the tebentafusp group. [8]

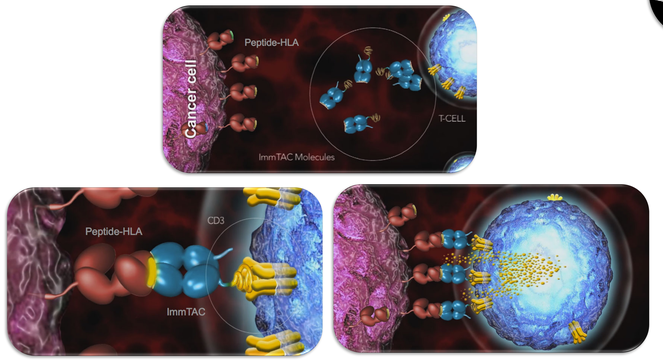


***Figure 2b**: Mechanism of action of tebentafusp. [9]*

Case Presentation

72-year-old female, a known metastatic Uveal melanoma. She was initially diagnosed in January 2017 and was subsequently treated with 2 lines of treatment with disease progression.

Tebentafusp was used under early access programme by provided by Immunocore. Treatment started on 14th Dec 2021; Starting dose 20mcg on Day 1, 30mcg on Day 8 followed by 68mcg. There was a partial response initially which has been followed by stable disease till the latest staging scan performed in September 2023. She has received a total of 97 weeks of treatment with good tolerance of treatment apart from mild rash during 2nd cycle and occasional sickness.

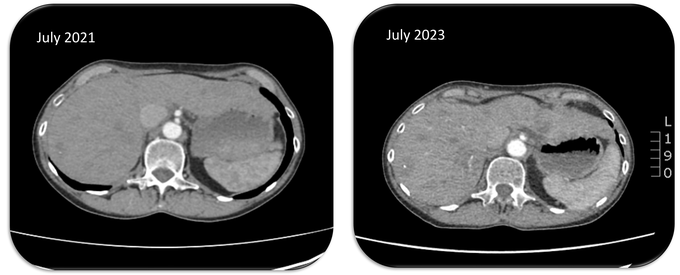


***Figure 3**: Comparison of pre-treatment and 20-month post-treatment liver CT Scan*

Conclusion

Tebentafusp can be considered as a viable treatment option to slow the disease progression and prolong life, warranting further research and potential consideration as a 2nd or 3rd line treatment option for previously treated metastatic uveal melanoma (mUM). Given the limited options for treatment of metastatic uveal melanoma, Tebentafusp stands as a hopeful addition to the treatment armamentarium, providing insights into its efficacy and paving the way for enhanced understanding of its mechanisms for the broader benefit of patients facing this challenging malignancy.

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