15-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
124975	**Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)** **Nivolumab**	**September 16, 2021**

4. SPONSOR

Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION	6. PHONE NUMBER
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8a. PROTOCOL NUMBER (AE #)	8b. AE GRADE: AE
EA6134 (AE #2812676)	**Grade 3: Retinal detachment** **Grade 3: Uveitis**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
46201	**69 years**	**Male**

12. PROTOCOL SPECIFIED

Induction Regimen 2: Cycles 1 & 2
Cycle = 42 Days
BMS-936558 (Nivolumab, MDX-1106): 3 mg/kg IV on Days 1 and 22
Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived): 1 mg/kg IV on Days 1 and 22

Maintenance: Cycles 3-14
BMS-936558 (Nivolumab, MDX-1106): 3 mg/kg IV on Days 1, 15, and 29

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on August 11, 2021, and received the first and only doses of ipilimumab and nivolumab that same day (Cycle 1, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 69-year-old male with malignant melanoma who developed grade 3 retinal detachment and grade 3 uveitis while on a Phase III trial utilizing the investigational agents ipilimumab and nivolumab. The patient has a history of hypertension. On August 25, 2021 (Cycle 1, Day 15), at a follow-up visit, the patient reported that he was seen at an urgent care facility 3-4 days prior for a stye/blepharitis at which time he was prescribed topical and oral antibiotics. He noted blurry vision in both eyes. Physical examination revealed inflamed eyelids with a stye on the right eye. Laboratory results were significant for a glucose of 107 mg/dL (reference range: 74-106 mg/dL) and an eosinophil percentage of 4.1% (reference range: 1.0-3.0%). The investigational agents were held pending evaluation by an ophthalmologist. On August 26, 2021, following an ophthalmology consult, the patient was diagnosed with panuveitis, serous retinal detachment, and a chalazion. He was prescribed difluprednate, cyclopentolate, neomycin/polymyxin B/dexamethasone ointment, prednisone, and cephalexin with a plan to follow-up in one week. At an oncology follow-up visit on September 1, 2021, the patient reported no ocular pain and improvement in vision. On September 3, 2021, at a follow-up visit with the ophthalmologist, his right eye examination showed significant improvement in the panuveitis. He reported not using the cyclopentolate as prescribed. Continuation of therapy was recommended with topical and oral steroid taper. Additional information has been requested from the investigational site.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442 = 8,467.
Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 720801 = 208.
Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 8,207.
There have been 2 other cases of retinal detachment reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There have been no other cases of retinal detachment reported to the NCI through CTEP-AERS as serious

15-DAY IND SAFETY REPORT

adverse events for ipilimumab under NSC 720801.
There has been 1 other case of retinal detachment (grade 3, unrelated) reported to the NCI through CTEP-AERS as a serious adverse event for nivolumab under NSC 748726.
Uveitis is an expected event for the investigational agents ipilimumab and nivolumab.

Adverse Event	Grade	Attribution
Ipilimumab (NSC 732442)		
Retinal detachment (n=2)	3	1 Possible, 1 Unrelated

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a probable relationship exists between the retinal detachment and uveitis and the investigational agents ipilimumab and nivolumab.

	Retinal detachment	Uveitis
Ipilimumab	**Probable**	**Probable**
Nivolumab	**Probable**	**Probable**
Melanoma	**Possible**	**Possible**
Probable Vogt-Koyanagi-Harada disease, VKH syndrome	**Possible**	**Possible**

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were erythromycin ointment, cephalexin, lisinopril, sulfamethoxazole-trimethoprim, and multivitamin.

18. COMMENTS

DISCLAIMER per 21 CFR 312.32(e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB MEDICAL OFFICER/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.