FOLLOW-UP IND SAFETY REPORT #1

1. IND NUMBER	2. AGENT NAME	3. DATE
124975	Nivolumab Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)	**January 22, 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
EA6141 (AE #2656714)	Grade 4: Blurred vision Grade 4: Vision decreased Grade 3: Retinopathy

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
16261	38 years	Female

12. PROTOCOL SPECIFIED

Cycle: 21 days (Induction Phase = 4 cycles)
Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived): 3 mg/kg IV over 90 minutes on Day 1
BMS-936558 (Nivolumab, MDX-1106): 1 mg/kg IV over 60 minutes on Day 1
GM-CSF (sargramostim, Leukine): 250 ug SQ, Days 1-14

Cycle: 21 Days (Maintenance Phase)
BMS-936558 (Nivolumab, MDX-1106): 3 mg/kg IV, Day 1
GM-CSF (sargramostim, Leukine): 250 ug SQ, Days 1-14

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on December 16, 2020, and received the first and only doses of nivolumab and ipilimumab on that same day (Cycle 1, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 38-year-old female with melanoma of the scalp who experienced grade 4 blurred vision, a grade 4 vision decrease, and grade 3 retinopathy while on a Phase II/III trial utilizing the investigational agents nivolumab and ipilimumab. Additional information has been requested from the investigational site.

The Initial Written Report was sent to the FDA on January 14, 2021, as a 7-day report.

<u>Follow-Up #1:</u>

On September 26, 2019, the patient underwent radical resection of her scalp vertex malignant melanoma with 2 cm margins. She underwent follow-up CT scans in November 2020, which were concerning for recurrence, revealing a new adrenal nodule and a cervical lymph node. These were confirmed by PET scans as sites of metastatic disease. On December 30, 2020, the patient reported having blurred vision and was seen by an ophthalmologist, who recommended artificial tears for dry eyes. On January 1, 2021, she presented to the emergency department (ED) due to recent vision changes. She reported waking up with blurred vision three days prior, which initially improved, but later worsened. In the ED, she complained of

right>left vision changes including blurry vision but denied having any previous vision problems. She stated that the day before she had blurred vision in her right eye involving anything beyond 5 feet, which worsened to having blurred vision at any distance beyond 2 feet. In her left eye, she described macular sparring with clear vision only in a decreased central circle. The patient also endorsed mild discomfort in her right eye, but denied any recent headaches, fevers, sore throat, or rash. She had a temperature of 98.4°F, blood pressure of 149/88 mmHg, heart rate of 100 beats per minute, respiratory rate of 18 breaths per minute, and an oxygen saturation (SpO_2) of 99%. Physical examination revealed no visual field deficits. An MRI scan of the brain was unremarkable for acute intracranial findings. That day, the patient was admitted for further observation. On January 2, 2021, she was seen by an ophthalmologist and underwent a fundus examination which revealed hypopigmented lesions of unclear significance at the far temporal aspect of the macula. The ophthalmologist felt that the patient's symptoms including ocular toxicity were possibly related to her immunotherapy. They recommended continuing daily prednisone and dexamethasone ophthalmic solution 4 times daily. On January 3, 2021, the patient reported some improvement in visual clarity in her left eye but had no improvement in the right eye. She was discharged home with a plan to follow-up with the ophthalmologist the next day. On January 4, 2021, patient called to report an area of obstructed vision in her right eye with flashes around it. The treating physician increased her dose of prednisone to 60mg daily. On January 5, 2021, the patient was seen by a retinal specialist who diagnosed her with serous retinopathy (right> left). The ophthalmic exam showed a visual acuity of 20/60 in her right eye and 20/20 in her left eye. On January 6, 2021, she was seen by the treating physician, who held prednisone and planned for restaging scans. That day, the patient was removed from the study treatment. On January 11, 2021, the patient was restarted on prednisone for persistent myalgias and nausea. By January 19, 2021, the patient's blurred vision had resolved.

15. ACCRUAL AND IND EXPERIENCE

~~Pending Follow-up report.~~

Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442 = 7,770.
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= 6,942.
Blurred vison is an expected event for nivolumab.
There have been 2 other cases of retinopathy reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
There have been no other cases of vision loss reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
There has been 1 other case of retinopathy reported to the NCI through CTEP-AERS as a serious adverse event for ipilimumab under NSC 732442.
There have been 11 other cases of blurred vision reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There have been no other cases of vision loss reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There have been no other cases of blurred vision, retinopathy or vision loss reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801.

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
Retinopathy (n=2)	4 3	1 Possible 1 Probable

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Ipilimumab (NSC 732442)		
Retinopathy (n=1)	**4**	**1 Possible**
Blurred vision (n=11)	**3** **2**	**1 Probable** **2 Definite, 2 Probable, 5 Possible, 1 Unlikely**

16. ASSESSMENT

~~Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship between the blurred vision, the vision decrease and the retinopathy and the investigational agents nivolumab and ipilimumab cannot be excluded. The adverse events and attributions will be reassessed when additional information becomes available.~~

Based on the provided medical documentation and our medical and scientific knowledge, a probable relationship exists between the blurred vision, the vision decrease, and the retinopathy and the investigational agents ipilimumab and nivolumab.

	Blurred vision	Vision decreased	Retinopathy
Ipilimumab	**Probable**	**Probable**	**Probable**
Nivolumab	**Probable**	**Probable**	**Probable**
Sargramostim	**Unrelated**	**Unrelated**	**Unrelated**
Melanoma	**Unlikely**	**Unlikely**	**Unlikely**

17. CONCOMITANT MEDICATIONS

~~Pending Follow-up report~~.

Medications taken at the time of the event were fluticasone propionate and bone stimulator

18. COMMENTS

~~Pending Follow-up report.~~

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.