# 15-DAY IND SAFETY REPORT

| 1. IND NUMBER | 2. AGENT NAME | 3. DATE |
|---|---|---|
| **129803** | **Nivolumab**<br>**XL184 (Cabozantinib)** | **April 21, 2022** |

4. SPONSOR

**Division of Cancer Treatment and Diagnosis, National Cancer Institute**

| 5. REPORTER'S NAME, TITLE, AND INSTITUTION | 6. PHONE NUMBER |
|---|---|
| **John Wright, MD, PhD – Associate Branch Chief, Investigational Drug Branch, CTEP, DCTD, NCI**<br><br>**Howard Streicher, MD – Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI** | **240-276-6565**<br>7. EMAIL ADDRESS<br>**ctepsupportae@tech-res.com** |

| 8a. PROTOCOL NUMBER (AE #) | 8b. AE GRADE: AE |
|---|---|
| **A031704 (AE #2121446)** | **Grade 3: Eye disorders - Optic neuritis; bilateral eyes** |

| 9. PATIENT IDENTIFICATION | 10. AGE | 11. SEX |
|---|---|---|
| **9136068** | **41 years** | **Female** |

12. PROTOCOL SPECIFIED

**Cycle = 28 days**
**Nivolumab (BMS-936558, MDX-1106): 480 mg IV on Day 1**
**XL184 (Cabozantinib): 40 mg PO QD**

13. TREATMENT RECEIVED AND DATES

**The patient began the investigational therapy on May 20, 2021, and received the last dose of nivolumab on September 13, 2021, and the last dose of cabozantinib on November 17, 2021 (Cycle 8, Day 13).**

14. DESCRIPTION OF ADVERSE EVENT

**The patient is a 41-year-old female with metastatic clear cell renal cell adenocarcinoma with sarcomatoid features of the left kidney (status post left nephrectomy in February 2021), who developed grade 3 bilateral optic neuritis while on a Phase III trial utilizing the investigational agents nivolumab and cabozantinib. The patient has a history of arthritis, and depressive episodes. Of note, the patient had reported peripheral vision loss in the right eye since October 25, 2021. On November 7, 2021, an MRI of the brain did not show any evidence of intracranial metastatic lesions or periorbital abnormalities. On November 11, 2021, the patient was seen by her optometrist at which time she was diagnosed with bilateral nonarthritic ischemic optic neuropathy which has caused significant visual field loss. She had an intraocular pressure of 16 mmHg in the right eye and 15 mmHg in the left eye. The investigational agent cabozantinib was continued, while nivolumab was held pending evaluation by an ophthalmologist. On November 16, 2021, an MRI of the orbit, face, and neck with contrast showed small symmetric optic nerve effusions bilaterally and mild mucosal thickening of the right sphenoid sinus without any evidence of an orbital mass or optic nerve enhancement. On November 23, 2021, following a neuro-ophthalmology consult, the patient was diagnosed with optic neuritis related to nivolumab therapy, but no treatment was prescribed. At an oncology follow-up visit on November 29, 2021, the patient reported improvement in her symptoms. That day, a decision was made to discontinue nivolumab with a plan to continue single agent therapy with cabozantinib. Additional information has been requested from the investigational site.**

15. ACCRUAL AND IND EXPERIENCE

**Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 9,113. Number of patients enrolled in NCI-sponsored clinical trials using cabozantinib under NSC 761968 = 2,508. There have been no other cases of bilateral optic neuritis reported to the NCI through CTEP-AERS as**

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**serious adverse events for nivolumab under NSC 748726.**
**There have been no other cases of bilateral optic neuritis reported to the NCI through CTEP-AERS as serious adverse events for cabozantinib under NSC 761968.**

16. ASSESSMENT

**Based on the provided medical documentation and our medical and scientific knowledge, a probable relationship exists between the bilateral optic neuritis and the investigational agent nivolumab.**
**The bilateral optic neuritis is not related to the investigational agent cabozantinib.**

| | Bilateral optic neuritis |
|---|---|
| **Nivolumab** | **Probable** |
| **Cabozantinib** | **Unlikely** |
| **Clear cell renal cell adenocarcinoma** | **Possible** |

17. CONCOMITANT MEDICATIONS

**Medications taken at the time of the event were budesonide, duloxetine, bupropion, diphenhydramine, dicyclomine, loperamide, ondansetron, and prochlorperazine maleate.**

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.**