15-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
126146	**Nivolumab**	**November 23, 2021**

4. SPONSOR

Division of Cancer Treatment and Diagnosis, National Cancer Institute

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

8a. PROTOCOL NUMBER (AE #)	8b. AE GRADE: AE
NRG-HN005 (AE #2606703)	**Grade 3: Cardiac disorders: Cardiomyopathy** **Grade 2: Ventricular tachycardia**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
CA141-HN005-00143	**61 years**	**Male**

12. PROTOCOL SPECIFIED

Nivolumab (BMS-936558, MDX-1106): 240 mg IV on Day 1 of weeks -1, 2, 4, 6, 8 and 10
RT: 2 Gy fractions on Days 1-6 each week for 5 weeks beginning on week 1 (total dose = 60 Gy in 30 fractions)

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on February 22, 2021, received the last dose of radiation on April 2, 2021, and received the last dose of nivolumab on May 3, 2021.

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 61-year-old male with squamous cell carcinoma of the tongue who developed grade 3 cardiomyopathy and grade 2 ventricular tachycardia while on a Phase II/III trial utilizing the investigational agent nivolumab in combination with radiotherapy. The patient has a history of hypothyroidism, coronary artery disease, cardiomyopathy, atrial fibrillation, hyperlipidemia, myxomatous mitral valve, severe mitral regurgitation status post mitral valve repair, and is a former smoker. On October 30, 2021, the patient was found to have 125 episodes of wide complex tachycardia lasting up to 46 seconds and some episodes of atrial fibrillation with aberrancy on Zio® patch heart monitor. The patient was referred to the emergency department (ED) by the cardiologist. Upon arrival to the ED, the patient was asymptomatic. Laboratory results were significant for a thyroid stimulating hormone (TSH) of 15.90 (reference range: 0.450-4.500 uIU/mL), white blood cell count of 3 K/uL (reference range: 4-11 K/uL) and a platelet count of 112 K/uL (reference range: 150-400 K/uL). He was admitted to the cardiology unit for further evaluation. On October 31, 2021, the patient was started on metoprolol and IV heparin. On November 1, 2021, a coronary angiogram revealed no angiographic evidence of obstructive coronary disease. On November 2, 2021, a cardiac MRI showed evidence of patchy diffuse mesocardial enhancement most pronounced in the basal septum and inferior wall with a pattern of nonischemic cardiomyopathy with possible etiologies including myocarditis *vs* chemotherapy induced injury or an infiltrative process such as amyloidosis. It also showed a dilated left ventricle with globally moderately reduced left ventricular ejection fraction of 37% and a reduced right ventricular ejection fraction of 41%. On November 3, 2021, the patient had a biventricular implantable cardioverter defibrillator (BiV ICD) placed with no complications. A right ventricular cardiac biopsy revealed marked myocyte hypertrophy, fibrosis, and was negative for lymphocytic myocarditis. Laboratory results showed troponin I levels of 0.062 ng/mL (reference range: <0.005 ng/mL). On November 4, 2021, the patient was started on prednisone 60mg for 5 days with a 4-week tapering dose. That day, the patient was discharged home in stable condition with plans to continue metoprolol and prednisone,

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start apixaban, and follow-up with the cardiologist. On November 17, 2021, the patient presented to the cardiologist for a scheduled follow-up visit. Physical examination was unremarkable. Laboratory results showed troponin I levels of 0.026 and TSH of 8.44. His metoprolol dose was increased, and he was advised to follow up in 2 months. Additional information has been requested from the investigational site.

15. ACCRUAL AFND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 8,568.
There have been 7 other cases of cardiomyopathy reported to the NCI through CTEP-AERS as a serious adverse event for nivolumab under NSC 748726.
There has been 1 other case of ventricular tachycardia (grade 3, possible) reported to the NCI through CTEP-AERS as a serious adverse event for nivolumab under NSC 748726.

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
Cardiomyopathy (n=7)	5 4 3 1	1 Probable 1 Unlikely 4 Probable 1 Possible

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the cardiomyopathy and the ventricular tachycardia and the investigational agent nivolumab.

	Cardiomyopathy	Ventricular tachycardia
Nivolumab	**Possible**	**Possible**
Radiation	**Unlikely**	**Unrelated**
Pharyngeal (including Hypopharyngeal and Oropharyngeal) squamous cell carcinoma	**Unlikely**	**Unlikely**
Pre-existing cardiomyopathy	**Definite**	**Probable**
Hypothyroid (elevated TSH)	**Possible**	**Possible**

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were levothyroxine, clindamycin powder, sacubitril-valsartan, sodium fluoride dental gel, chlorhexidine oral rinse, calcium carbonate-vitamin D, vitamin C, levomefolate glucosamine, and coenzyme Q.

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.