# 7-DAY IND SAFETY REPORT

| 1. IND NUMBER | 2. AGENT NAME | 3. DATE |
|---|---|---|
| **137444** | **Anetumab ravtansine (BAY 94-9343)**<br>**Nivolumab** | **October 21, 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**<br><br>**Jeffrey Moscow, MD – Branch Chief, 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 |
|---|---|
| **10208 (AE # 2937629)** | **Grade 5: Multiorgan failure**<br>**Grade 4: Hepatic failure**<br>**Grade 4: Heart failure** |

| 9. PATIENT IDENTIFICATION | 10. AGE | 11. SEX |
|---|---|---|
| **CA088-0175** | **73 years** | **Male** |

12. PROTOCOL SPECIFIED

**Cycle = 28 days, Cycle 1**
**Anetumab ravtansine (BAY 94-9343): 6.5 mg/kg IV on Day 1**
**Nivolumab (BMS-936558, MDX-1106): 360 mg IV on Day 8**
**Gemcitabine hydrochloride: 1000 mg/m$^2$ IV on Day 1 and 8**

**Cycle = 21 days, Cycle 2+**
**Anetumab ravtansine (BAY 94-9343): 6.5 mg/kg IV on Day 1**
**Nivolumab (BMS-936558, MDX-1106): 360 mg IV on Day 1**
**Gemcitabine hydrochloride: 1000 mg/m$^2$ IV on Day 1 and 8**

13. TREATMENT RECEIVED AND DATES

**The patient began the investigational therapy on May 18, 2021, and received the last doses of anetumab ravtansine and nivolumab on August 17, 2021 (Cycle 5, Day 1).**

14. DESCRIPTION OF ADVERSE EVENT

**The patient was a 73-year-old male with adenocarcinoma of the pancreas status post distal pancreatectomy with splenectomy (2019), who developed grade 4 hepatic failure and grade 4 heart failure, and later expired on September 6, 2021, due to multiorgan failure while on a Phase I trial utilizing the investigational agents anetumab ravtansine and nivolumab in combination with gemcitabine. The patient had a history of diabetes mellitus type 2, peripheral neuropathy, hypertension, and gastric ulcer. Of note, he completed radiation therapy with Yttrium-90 to the left hepatic artery in March 2021. On August 30, 2021, he presented to the emergency department (ED) with generalized weakness following a near syncopal episode, which occurred prior to arrival. He had a blood pressure of 125/85 mmHg, heart rate of 81 beats per minute, temperature of 97.8°F, respiratory rate of 16 breaths per minute, and an oxygen saturation ($SpO_2$) of 96% on room air. On physical exam, he was frail and had conjunctival pallor. Laboratory results were significant for a troponin I of <0.015 ng/mL (reference range: 0-0.100 ng/mL), glucose of 62 mg/dL (reference range: 60-100 mg/dL), hemoglobin of 10.7 gm/dL (reference range: 13.0-18.0 gm/dL), alanine aminotransferase (ALT) of 100 U/L (reference range: 0-38 U/L), aspartate aminotransferase (AST) of 133 U/L (reference range: 15-37 U/L), alkaline phosphatase (ALP) of 675 U/L (reference range: 45-117U/L), albumin of 2.4 gm/dL (reference range: 3.0-4.8 gm/dL), potassium of 3.0 mEq/L (reference range: 3.5-5.1 mEq/L), bicarbonate of 35 mEq/L (reference range: 21-33 mEq/L), blood urea nitrogen of 55 mg/dL (reference range: 7-18 mg/dL), and creatinine of 1.0mg/dL (reference range: 0.6-1.3 mg/dL). A COVID-19 PCR test was negative. An electrocardiogram (ECG) showed normal sinus rhythm. A chest X-ray showed minimal pleural effusions. A CT scan of the abdomen and pelvis with contrast showed a small cirrhotic liver, multiple subhepatic lesions, pleural effusions, large volume ascites, and cholelithiasis. The patient was started on intravenous fluids,**

**albumin, and oral potassium. He was admitted for further evaluation and cardiac monitoring. On August 31, 2021, the patient underwent an ultrasound-guided paracentesis, removing 3 L of ascitic fluid. The fluid contained no organisms or malignant cells. On September 1, 2021, an MRI of the abdomen with contrast showed cirrhosis with a diffusely low signal and heterogenous liver parenchyma, reflecting a combination of post embolization changes and iron overload. There was also evidence of diffuse gastric wall thickening, multiple T2 hyperdense lesions throughout the lumbar spine, and multifocal pneumonia with small pleural effusions (left > right). The treating physician felt that the bone lesions were likely osteoblastic reaction to treatment, and liver cirrhosis occurred due to late effect from radioembolization. On September 2, 2021, a CT of the chest showed dependent right lung pneumonia, minimal left upper lobe bronchopneumonia, small pleural effusions, mild interstitial edema, and diffuse soft tissue edema. That day, an echocardiogram showed aortic root dilatation, calcific aortic valvular disease without evidence of significant aortic stenosis, left atrial enlargement, severe left ventricular hypokinesia with an ejection fraction of 20%, moderate aortic regurgitation, moderate mitral regurgitation, mild pulmonic regurgitation, and moderate tricuspid regurgitation with a right ventricular systolic pressure of 40 mmHg. The treating physician felt that the congestive heart failure occurred in the context of multiorgan failure due to acute hepatic decompensation. He was started on piperacillin/tazobactam, doxycycline, heparin, spironolactone, and lactulose. The patient continued to have poor oral intake and severe malnutrition. On September 4, 2021, laboratory results were significant for a brain natriuretic peptide of > 5000 pg/mL (reference range: 0-100 pg/mL). On September 6, 2021, a lower extremity venous ultrasound showed no evidence of deep vein thrombosis. Following discussion with his family, the patient was discharged with home hospice care. Later that day, the patient expired. An autopsy was not performed.**

15. ACCRUAL AND IND EXPERIENCE

**Number of patients enrolled in NCI-sponsored clinical trials using anetumab ravtansine under NSC 791065 = 472**

**Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 8,466.**

**There have been 15 other cases of heart failure reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.**

**There have been 9 other cases of hepatic failure reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.**

**There has been no cases of multiorgan failure reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.**

**There have been no cases of heart failure, hepatic failure or multiorgan failure reported to the NCI through CTEP-AERS as serious adverse events for anetumab ravtansine under NSC 791065.**

| Adverse Event | Grade | Attribution |
|---|---|---|
| ***Nivolumab (NSC 748726)*** | | |
| Heart failure (n=15) | 5 | 1 Unlikely |
| | 4 | 1 Probable, 1 Possible, 1 Unlikely |
| | 3 | 2 Probable, 2 Possible, 2 Unrelated |
| | 2 | 1 Possible |
| | 1 | 2 Possible, 1 Unrelated |
| Hepatic failure (n=9) | 5 | 1 Unlikely |
| | 4 | 1 Probable |
| | 3 | 1 Definite, 1 Probable, 4 Possible, 1 Unlikely |

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16. ASSESSMENT

**Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the heart failure, hepatic failure, multi-organ failure and the investigational agent nivolumab. The heart failure, hepatic failure, and multi-organ failure are not related to the investigational agent anetumab ravtansine.**

| | Heart failure | Hepatic failure | Multi-organ failure |
|---|---|---|---|
| **Anetumab ravtansine** | **Unlikely** | **Unlikely** | **Unlikely** |
| **Nivolumab** | **Possible** | **Possible** | **Possible** |
| **Gemcitabine** | **Unlikely** | **Unlikely** | **Unlikely** |
| **Adenocarcinoma of the pancreas** | **Possible** | **Possible** | **Unlikely** |
| **Prior Yttrium-90 embolization (March 2021)** | **Unlikely** | **Possible** | **Unlikely** |

17. CONCOMITANT MEDICATIONS

**Medications taken at the time of the event were methadone, furosemide, metformin, omeprazole, famotidine, calcium carbonate, sucralfate, metoclopramide, ondansetron, and hydrocodone/acetaminophen.**

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.**