SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET		
		Day	Month	Year				Day	Month	Year
PRIVACY	Malaysia		PRIVACY		39 Years	Female	Unk	18	NOV	2019

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Pneumonia [Pneumonia]

Case Description: Case number# NVSC2019MY043068, is an initial report received from an investigator on 19 Nov 2019 from a clinical study CACZ885U2301. This report refers to a 39 year old female subject (center ID: XXX; subject ID: XXX) enrolled in a randomized, double blind, placebo controlled, phase III study evaluating the efficacy and safety of pembrolizumab plus platinum based doublet chemotherapy with or without canakinumab as first line therapy for locally advanced or metastatic non squamous and squamous non small cell lung cancer subjects (CANOPY 1).

(Continued on Additional Information Page)

- ☒ PATIENT DIED Date: 18-NOV-2019
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) COMPARATOR PEMETREXED (PEMETREXED DISODIUM) Powder for solution for infusion
#2) COMPARATOR PEMBROLIZUMAB (PEMBROLIZUMAB) Concentrate **(Continued on Additional Information Page)**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 675 mg	#1) Intravenous use
#2) 200 mg	#2) Intravenous use

17. INDICATION(S) FOR USE
#1) Non-small cell lung cancer (Non-small cell lung cancer)
#2) Non-small cell lung cancer (Non-small cell lung cancer)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 20-AUG-2019 / Unknown	#1) Unknown
#2) 20-AUG-2019 / Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) GRANISETRON (GRANISETRON) ; 20-AUG-2019 / Unknown
#2) OXYNORM (OXYCODONE HYDROCHLORIDE) ; 29-JUL-2019 / Unknown
#3) NORMAL SALINE (SODIUM CHLORIDE) ; 20-AUG-2019 / Unknown
#4) MAGNESIUM SULFATE (MAGNESIUM SULFATE) 50 %; 20-AUG-2019 / Unknown
#5) GABAPENTIN (GABAPENTIN) ; 05-NOV-2019 / Unknown
#6) PARACETAMOL (PARACETAMOL) ; 05-NOV-2019 / Unknown **(Continued on Additional Information Page)**

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Current Condition	Bone metastases (Metastases to bone)
Unknown to Ongoing	Current Condition	Pneumonia (Pneumonia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Novartis Pharmaceuticals Corp.

26. REMARKS
World Wide #: MY-002147023-NVSC2019MY043068

24b. MFR CONTROL NO.
NVSC2019MY043068

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
28-MAR-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
31-MAR-2023

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP: 7

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

The subject's historical conditions of the subject were not reported. The subject's current conditions included pneumonia and bone metastasis. Concomitant medications included augmentin, granisetron, Oxynorm (oxycodone hydrochloride), Normal Saline (sodium chloride), magnesium sulfate, gabapentin, paracetamol, pamidronate disodium, Targin (oxycodone hydrochloride, naloxone hydrochloride), Celebrex (celecoxib), folic acid, cyanocobalamin, potassium chloride, metoclopramide and mannitol. It was reported that the subject was on stage 4B. On 20 Aug 2019, the subject started blinded study medication. On the same date, started study medications pemetrexed at a dose of 675 mg (intravenous), pembrolizumab at a dose of 200 mg (intravenous) and carboplatin at a dose of 750 mg (intravenous). On 12 Nov 2019, the subject received the latest dose of blinded study medication prior to the event. On an unknown date, treatment with blinded study medication was discontinued. Since 14 Nov 2019, the subject was unwell and complained of fever and cough worsen. The subject did not inform site and went to GP (general practitioner) clinic.

On 18 Nov 2019, 2 months and 30 days after the first dose of the study medication, the subject was diagnosed with pneumonia. The subject was treated with Zinnat (cefuroxime axetil), however condition got worsened. The action taken with carboplatin, pembrolizumab and pemetrexed was unknown. On 18 Nov 2019, the subject died at 06:00 AM. The death was due to pneumonia. It was reported that an autopsy was not performed. The subject also complained of poor appetite but was able to walk, a day before she passed away. No laboratory tests were available as the subject passed away at home. The diagnosis event pneumonia (death) was considered serious by the investigator. No other possible contributory factor was reported for the event. Additional case for this subject was MY-002147023-NVSC2019MY016352.

The causality of pneumonia with blinded study medication, carboplatin, pembrolizumab and pemetrexed were reported as suspected. Causality to any other medication or non-drug therapy was reported as not suspected.

Follow up report received on 21 Jan 2020: Added hospitalization date (14 Nov 2019) and added information (subject was stage 4B).

Follow up report received on 18 Feb 2020: Added current conditions (bone metastasis, pain and neuropathic pain) and concomitant medications (granisetron, Normal Saline (sodium chloride), Magnesium (magnesium sulfate), gabapentin, paracetamol, pamidronate disodium, cyanocobalamin, dexamethasone, potassium chloride and mannitol).

Follow up report received on 04 Mar 2020: Added concomitant medication (metoclopramide) and SAE Death with details.

Follow up to open report received on 05 Mar 2020 (prior to circulation of this previous report): Deleted SAE death with details and updated onset date of SAE pneumonia from 14 Nov 2019 to 18 Nov 2019.

Follow up report received on 19 Aug 2021: Added dosage details for study medications (blinded study medication, carboplatin, pembrolizumab and pemetrexed).

Follow up report received on 01 Sep 2022: Updated concomitant medication zinnat to treatment medication. Added concomitant medication augmentin. Added causality to any other medication or non-drug therapy.

Follow up report received on 28 Mar 2023: Deleted action taken (not applicable) with carboplatin, pembrolizumab and pemetrexed.

Listedness information:-
1. Product --> ACZ885+Pembro+Platinum CTx or Placebo+Pembro+Platinum CTx, Event --> pneumonia, Causality --> Not assessable
Sheet Name --> IB
Listedness --> Unknown.
2. Product --> PEMBROLIZUMAB, Event --> pneumonia, Causality --> Not assessable
Sheet Name --> IB
Listedness --> Unlisted.
3. Product --> PEMETREXED, Event --> pneumonia, Causality --> Not assessable
Sheet Name --> IB
Listedness --> Unlisted.
4. Product --> CARBOPLATIN, Event --> pneumonia, Causality --> Not assessable
Sheet Name --> IB
Listedness --> Listed.

Novartis Comment: This 39-year-old female subject with non-small cell lung cancer developed fatal pneumonia around 3 months after starting blinded study medication (ACZ885 vs Placebo), Pembrolizumab, Pemetrexed and Carboplatin. Pneumonia can develop as a complication of advanced lung cancer with fatal outcome. There is limited information pertaining to the medical history of the subject (h/o COPD, CHF, Asthma), etiological diagnosis of the event, relevant investigations (Chest X Ray, CT Scan Lung, CBC, and sputum analysis), and autopsy reports. Considering the missing information and strong confounder, it precludes a meaningful medical assessment for the event of pneumonia with all study drugs. Case will be reassessed after accrual of follow-up information.

Mfr. Control Number: NVSC2019MY043068

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Weight Significant	33 kg	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#2) COMPARATOR PEMBROLIZUMAB (PEMBROLIZUMAB) Concentrate for solution for infusion; Regimen #1	200 mg; Intravenous use	Non-small cell lung cancer (Non-small cell lung cancer)	20-AUG-2019 / Unknown; Unknown
#3) COMPARATOR CARBOPLATIN (CARBOPLATIN) Concentrate for solution for infusion; Regimen #1	750 mg; Intravenous use	Non-small cell lung cancer (Non-small cell lung cancer)	20-AUG-2019 / Unknown; Unknown
#4) ACZ885+Pembro+Platinum CTx or Placebo+Pembro+Platinum CTx (XXX); Regimen #1	XXX:XX	Non-small cell lung cancer (Non-small cell lung cancer)	20-AUG-2019 / 12-NOV-2019; 2 months 24 days

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) PAMIDRONATE DISODIUM (PAMIDRONATE DISODIUM) ; 12-NOV-2019 / Unknown

#8) TARGIN (OXYCODONE HYDROCHLORIDE, NALOXONE HYDROCHLORIDE) ; 27-AUG-2019 / Unknown

#9) CELEBREX (CELECOXIB) ; 27-AUG-2019 / Unknown

#10) FOLIC ACID (FOLIC ACID) Syrup ; 08-AUG-2019 / Unknown

#11) CYANOCOBALAMIN (CYANOCOBALAMIN) ; 08-AUG-2019 / Unknown

#12) POTASSIUM CHLORIDE (POTASSIUM CHLORIDE) 10 %; 20-AUG-2019 / Unknown

#13) METOCLOPRAMIDE (METOCLOPRAMIDE) ; 12-NOV-2019 / Unknown

#14) MANNITOL (MANNITOL) 20 %; 20-AUG-2019 / Unknown

#15) AUGMENTIN (AMOXICILLIN) ; 06-OCT-2019 / 12-OCT-2019