1. SYNOPSIS/ABSTRACT

TITLE

A NON-INTERVENTIONAL STUDY TO INVESTIGATE THE EFFECTIVENESS, SAFETY AND UTILIZATION OF COBIMETINIB AND VEMURAFENIB IN PATIENTS WITH AND WITHOUT BRAIN METASTASIS WITH BRAF V600 MUTANT MELANOMA UNDER REAL WORLD CONDITIONS

(coveNIS)

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KEYWORDS

Malignant melanoma; Brain metastases; BRAF V600 mutation; Vemurafenib / Cobimetinib; Non-interventional study.

RATIONALE AND BACKGROUND

Cobimetinib combined with vemurafenib is approved for the treatment of adult patients with unresectable or metastatic malignant melanoma (mM) with a BRAF V600 mutation. No comprehensive data on effectiveness, safety and utilization of this drug combination in daily clinical routine in Germany are available. Furthermore, this non-interventional post-authorization safety study (NI-PASS) is part of the Cotellic EU Risk Management Plan (EU RMP) as a Category 3 commitment (MEA 003).

RESEARCH QUESTION AND OBJECTIVES

The aim of this NI-PASS was to provide data on effectiveness of cobimetinib plus vemurafenib with a focus on overall survival (OS), safety and utilization of the combination therapy in two cohorts: patients with unresectable or metastatic BRAF V600 mutant mM with or without cerebral metastases. A comparison between the two cohorts was not planned.

AMENDMENT AND UPDATES TO PROTOCOL

The initial protocol version was v1.1. Protocol v2.0 was never published. Protocol v3.0 including one amendment was the final protocol.

STUDY DESIGN

Prospective, multi-centre, two-cohort NI-PASS. The study included patients with an underlying diagnosis of BRAF V600 mutant unresectable or metastatic mM, either without (Cohort A) or with (Cohort B) cerebral metastases.

STUDY PERIOD

First Patient In: 21 June 2017.

Last Patient Last Visit (LPLV): 30 June 2021.

Length of study: 4 years. Patient recruitment: 31 months. Follow-up for a maximum of 18 months after end of therapy.

SETTING

32 centres in Germany.

SUBJECTS AND STUDY SIZE

The study observed patients with mM with a BRAF V600 mutation according to summary of products characteristics (SmPC) who had no previous treatment with BRAF- and/or MEK inhibitors prior to study entry.

coveNIS observed 95 patients in total (planned 225) who constituted both the core analysis population and the safety population (Cohort A: 54 patients, planned 157; Cohort B: 41 patients,

planned 68). There were no major differences in demographic characteristics between both cohorts.

VARIABLES AND DATA SOURCES

PRIMARY EFFECTIVENESS VARIABLE:

- OS

PRIMARY SAFETY VARIABLES:

- Total AEs
- SAEs
- Grade ≥3 AEs
- AEs leading to treatment discontinuation
- Adverse events of special interest (AESIs)

[redacted]

RESULTS

Median Treatment Duration:

	Cohort A (N=54)	Cohort B (N=41)	Total (N=95)
Length of time on treatment [days]			
Cobimetinib, median (range)	94.5 (8 - 916)	83.0 (5 - 691)	93.0 (5 - 916)
Vemurafenib, median (range)	107.5 (8 - 916)	83.0 (5 - 691)	98.0 (5 - 916)

Key Results Regarding the Primary and Secondary Objectives:

Objectives	Cohort A (N=54)	Cohort B (N=41)
Primary objective		
Median OS [95% CI] [months]	21.6 [11.1, NE]	7.4 [4.1, 11.5]
Secondary objectives		
Median PFS [95% CI] [months]	6.9 [4.9, 13.8]	5.2 [2.6, 8.3]
Median time to development of cerebral metastases [95% CI] (Cohort A) [months]	8.4 [5.8, 18.7]	-
Median time to CNS relapse [95% CI] (Cohort B) [months]	-	4.3 [2.6, 5.7]

CI = confidence interval; CNS = central nervous system; NE = not estimable (could not be calculated due to a too low number of events); OS = overall survival; PFS = progression-free survival.

As this study was a non-interventional study (NIS), the proposed assessments and their suggested timings in the observational plan were not mandatory. This led to few tumour assessments for ORR, iORR, eORR and a low return rate for patient-reported outcomes (PROs; EORTC QLQ-C30), hindering their reliable estimation.

Key Results Regarding the Safety Objectives:

Number of Patients with AEs Most frequent MedDRA Preferred Terms in		
Cohort A (N=54)	Cohort B (N=41)	Total (N=95)
Patients with any AEs		
45 (83.3%)	36 (87.8%)	81 (85.3%)
Diarrhoea: 20 (37.0%)	Diarrhoea: 15 (36.6%)	Diarrhoea: 35 (36.8%)
Vomiting: 11 (20.4%)	Fatigue: 9 (22.0%)	Pyrexia: 19 (20.0%)
Pyrexia: 11 (20.4%)	Pyrexia: 8 (19.5%)	Rash: 17 (17.9%)
Patients with AEs Grade ≥3		
31 (57.4%)	30 (73.2%)	61 (64.2%)
Pneumonia: 5 (9.3%)	Death: 4 (9.8%)	Pyrexia: 7 (7.4%)
Pyrexia: 5 (9.3%)	-	Diarrhoea: 6 (6.3%)
Diarrhoea: 4 (7.4%)	-	Pneumonia: 6 (6.3%)
Rash: 4 (7.4%)	-	-
Patients with SAEs		
28 (51.9%)	29 (70.7%)	57 (60.0%)
Pyrexia: 7 (13.0%)	Death: 4 (9.8%)	Pyrexia: 11 (11.6%)
Nausea: 5 (9.3%)	Pyrexia: 4 (9.8%)	Nausea: 7 (7.4%)
Pneumonia: 5 (9.3%)	Acute kidney injury: 3 (7.3%)	Diarrhoea: 6 (6.3%)
	Seizure: 3 (7.3%)	Pneumonia: 6 (6.3%)
Patients with ADRs related to cobimetinib and vemurafenib		
31 (57.4%)	20 (48.8%)	51 (53.7%)
Diarrhoea: 12 (22.2%)	Diarrhoea: 7 (17.1%)	Diarrhoea: 19 (20.0%)
Pyrexia: 8 (14.8%)	Rash: 5 (12.2%)	Rash: 12 (12.6%)
Rash: 7 (13.0%)	Fatigue: 4 (9.8%)	Pyrexia: 10 (10.5%)
Vomiting: 7 (13.0%)	Photosensitivity reaction: 4 (9.8%)	-
-	Solar dermatitis: 4 (9.8%)	-
Patients with AEs leading to treatment discontinuation		
30 (55.6%)	24 (58.5%)	54 (56.8%)
Diarrhoea: 10 (18.5%)	Diarrhoea: 5 (12.2%)	Diarrhoea: 15 (15.8%)
Rash: 7 (13.0%)	Pyrexia: 5 (12.2%)	Pyrexia: 10 (10.5%)
Pyrexia: 5 (9.3%)	Fatigue: 3 (7.3%)	Rash: 9 (9.5%)
-	Nausea: 3 (7.3%)	-

Number of Patients with AEs Most frequent MedDRA Preferred Terms in		
Cohort A (N=54)	Cohort B (N=41)	Total (N=95)
Patients with AEs leading to death		
5 (9.3%)	8 (19.5%)	13 (13.7%)
Sepsis: 3 (5.6%)	Death: 4 (9.8%)	Death: 5 (5.3%)
Death: 1 (1.9%)	-	Sepsis: 3 (3.2%)
Pneumonia: 1 (1.9%)	-	-
Patients with AESIs		
11 (20.4%)	11 (26.8%)	22 (23.8%)
AESI 'Rash, Grade ≥3': 10 (18.5%)	AESI 'Rash, Grade ≥3': 4 (9.8%)	AESI 'Rash, Grade ≥3': 14 (14.7%)
AESI 'Grade ≥3 haemorrhage events or any grade cerebral haemorrhage': 2 (3.7%)	AESI 'Potential medicine-induced liver injury': 3 (7.3%)	AESI 'Potential medicine-induced liver injury': 4 (4.2%)
Patients with SMQ haemorrhages narrow search terms		
7 (13.0%)	3 (7.3%)	10 (10.5%)
Epistaxis: 2 (3.7%)	-	Epistaxis: 2 (2.1%)

ADR = adverse drug reaction; AE = adverse event; AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SAE = serious adverse event; SMQ = Standardized MedDRA query.

Note: In general, the three most frequent Preferred Terms (PTs) are shown for every type of AE. Exceptions to this may arise if more than one PT was reported for the same number of patients (more than three PTs shown) or if PTs were reported for only one or two patients (fewer than three PTs shown).

DISCUSSION

The data obtained in this study provide an important information about effectiveness, safety and utilization of cobimetinib plus vemurafenib for the treatment of adult patients with unresectable or metastatic mM with a BRAF V600 mutation, without (Cohort A) and with (Cohort B) cerebral metastases, in routine clinical practice in Germany. A direct comparison between Cohort A and Cohort B was not intended.

The effectiveness results for mM patients without cerebral metastases (Cohort A) were in line with the clinical benefit of the combined cobimetinib and vemurafenib therapy known from the pivotal study coBRIM. The effectiveness results for mM patients with cerebral metastases (Cohort B) were in line with previously observed clinical benefit of other targeted therapies.

The safety results in Cohort A and Cohort B were in line with the known safety profile of cobimetinib plus vemurafenib. Some AEs in Cohort B could be attributed to the presence of brain metastases.

However, the general limitations of a NIS apply (e.g. non-mandatory assessments, sample size).

CONCLUSION

In Cohort A, the patients benefited from the therapy and no new safety signals were observed. These results support the known benefit-risk ratio of treatment with cobimetinib plus

vemurafenib in a real world setting in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma without brain metastases.

Malignant melanoma patients with active cerebral metastases are often excluded from clinical studies. Data evaluating effectiveness and safety of treatment with cobimetinib plus vemurafenib are missing in this patient subset. In Cohort B, the OS results are in line with findings on similar treatments with targeted therapies for BRAF V600 mutation-positive mM in patients with cerebral metastases. This implies some OS improvement for this patient subset, acknowledging that patients with cerebral metastases remain at worse prognosis compared to patients with only extracranial disease. No new safety signals were observed in Cohort B.

Collectively, coveNIS provides real world evidence that cobimetinib plus vemurafenib therapy represents a favourable and safe treatment option with positive effects on disease control and survival outcomes for patients with BRAF V600 mutation-positive mM both without and with brain metastases.

MARKETING AUTHORIZATION HOLDER(S)

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