OPEN

Effectiveness, safety and utilization of cobimetinib and vemurafenib in patients with BRAF V600 mutant melanoma with and without cerebral metastasis under real-world conditions in Germany: the non-interventional study coveNIS

Katharina C. Kähler[a], Dirk Debus[b], Gaston Schley[c], Daniela Göppner[d], Jessica C. Hassel[e], Friedegund Meier[f], Patrick Terheyden[g], Rudolf Stadler[h], Thomas Tüting[i], Martin Kaatz[j], Norman-Philipp Hoff[k], Ehsan Masoudi[l], Agnieszka Zdanowicz-Specht[l], Minh Tam Nguyen[l] and Peter Mohr[m]

Cobimetinib/vemurafenib combination therapy is approved for treatment of adults with unresectable or metastatic BRAF V600 mutated malignant melanoma (mM). The non-interventional post-authorisation safety study coveNIS collected real-world data on cobimetinib/vemurafenib treatment focussing on overall survival (OS), safety and utilization. MM patients with brain metastases are usually excluded from clinical studies. coveNIS observed 2 cohorts: mM patients without (Cohort A) and with cerebral metastases (Cohort B), aiming to close the data gap for the latter population. A direct comparison of the 2 cohorts was not intended. The primary effectiveness objective was OS; the safety objective was the incidence of all and of serious adverse events (AEs). Secondary objectives included progression-free survival (PFS), time to development of cerebral metastasis (Cohort A) and time to central nervous system relapse (Cohort B). All statistical analyses were descriptive. Between 2017 and 2021, 95 patients were included (Cohort A: 54, Cohort B: 41 patients) at 32 sites in Germany. Median OS was 21.6 months in Cohort A, 7.4 months in Cohort B. Median PFS was 6.9 months in Cohort A, 5.2 months in Cohort B. The proportion of patients experiencing any AEs was 83.3% (Cohort A) and 87.8% (Cohort B). The two most common AEs in Cohort A were 'diarrhoea' (37%), 'vomiting' (20.4%) and 'pyrexia' (20.4%); in Cohort B 'diarrhoea' (36.6%) and 'fatigue' (22%). In conclusion, the OS rates in Cohort A and Cohort B of coveNIS are in line with the OS data from other trials with BRAF/MEK inhibitors for mM. No new safety signals were observed. *Melanoma Res* **34: 44–53 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.**

Melanoma Research 2024, **34**:44–53

Keywords: BRAF V600 mutation, brain metastases, cobimetinib, malignant melanoma, non-interventional study, vemurafenib

[a]UKSH Schleswig-Holstein, Campus Kiel, Klinik für Dermatologie Venerologie und Allergologie, Kiel, [b]Klinikum Nürnberg, Hautklinik, Universitätsklinik für Dermatologie der Paracelsus Medizinischen Privatuniversität, Nürnberg, [c]HELIOS Klinikum Schwerin und universitärer Campus der MSH-Medical School Hamburg, Hautklinik, Schwerin, [d]Universitätsklinikum Gießen, Klinik für Dermatologie Venerologie und Allergologie, Gießen, [e]Universitätsklinikum Heidelberg, Hautklinik und Nationales Centrum für Tumorerkrankungen, Heidelberg, [f]Klinik und Poliklinik für Dermatologie, Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Hauttumorzentrum am Nationalen Centrum für Tumorerkrankungen und Universitäts KrebsCentrum Dresden, Dresden, [g]UKSH Schleswig-Holstein, Campus Lübeck, Klinik für Dermatologie Allergologie und Venerologie, Lübeck, [h]Universitätsklinik für Dermatologie, Johannes Wesling Klinikum, Minden, Klinikum der Ruhr-Universität Bochum (UK-RUB), [i]Universitätshautklinik Magdeburg, Klinik für Dermatologie und Venerologie, Magdeburg, [j]SRH Wald-Klinikum gGmbH, Klinik für Hautkrankheiten und Allergologie, Gera, [k]Universitätsklinikum Düsseldorf, Klinik für Dermatologie, Düsseldorf, [l]Roche Pharma AG, Grenzach-Wyhlen and [m]Elbe Klinikum Buxtehude, Klinik für Dermatologie, Buxtehude, Germany

Correspondence to Dr. Peter Mohr, Elbe Klinikum Buxtehude, Klinik für Dermatologie, Am Krankenhaus 1, 21614 Buxtehude, Germany
Tel: +49 4161 7036250; e-mail: Peter.Mohr@elbekliniken.de

Received 22 December 2022 **Accepted** 21 May 2023.

Introduction

Cutaneous malignant melanoma (mM) is a malignant disease of melanocytes, located primarily in the basal layer of the epidermis [1]. In 2018, about 22 890 new cases were diagnosed in Germany and the incidence is projected to increase in the coming years [2]. The prognosis, namely survival rate, of mM depends on the stage of the disease. The observed 5-year melanoma-specific survival rates of patients with American Joint Committee on Cancer (AJCC) stage IIIA, IIIB, IIIC and IIID disease are 93%, 83%, 69% and 32%, respectively [3]. For AJCC stage IV, that is, patients with distant metastases, no subgroups were proposed and no survival rates were analysed [3].

Until 2011, chemotherapy with cisplatin and vindesine, with no proven benefit on overall survival (OS), comprised the only approved and systemic treatment for metastatic mM in Germany [4]. The introduction of new immunotherapeutic agents, as well as targeted therapies for patients with BRAF mutant mM offer potent

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.melanomaresearch.com.

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

treatment options to patients. The 2 major therapeutic breakthroughs in this regard comprise application of immune checkpoint inhibitors (ICI) and targeted therapy [5]. Ipilimumab, a monoclonal cytotoxic T lymphocyte-associated protein 4 antibody and its successors nivolumab and pembrolizumab represent such ICIs with enhanced potency [5]. In patients with previously untreated advanced melanoma, the combination of nivolumab and ipilimumab or nivolumab alone have been shown to have superior efficacy compared to ipilimumab alone [6]. An example of individualized targeted therapy is BRAF inhibition (BRAFi) and, more recently, combined BRAF/MEK inhibition (BRAFi/MEKi), targeting additionally the mitogen-activated protein kinase pathway. Mutations in the BRAF gene account for 40–60% of oncogenic driver mutations in mM [7,8]. Combination therapy of MEKi cobimetinib and BRAFi vemurafenib has demonstrated superior efficacy in patients with mutations in BRAF V600E or V600K compared to vemurafenib monotherapy [5].

Patients with advanced mM frequently develop brain metastases. Around 10% of initially diagnosed mM patients present with brain metastases [9,10]. The cumulative incidence of brain metastases after 5 years was estimated at 7.4% in patients with mM [9]. Over the course of the disease, the risk for brain metastasis increases. Autopsy series have reported up to 75% of mM patients having brain metastases [11]. In a pilot study, patients with BRAF V600 metastatic mM and previously treated, unresectable brain metastases, requiring corticosteroids for symptom control were treated with vemurafenib monotherapy [12]. Median OS was 5.3 months, and median progression-free survival (PFS) in the brain was 4.3 months [12]. Other trials with BRAFi monotherapy reported similar efficacy for patients with brain metastases that was inferior to patients without cerebral metastases [13,14]. Commonly, mM patients with central nervous system (CNS) involvement are excluded from clinical trials [15].

The ABC study, an open-label phase II trial, suggests that patients with untreated asymptomatic brain metastases benefit from immunotherapy with nivolumab/ipilimumab, which was therefore proposed as first-line therapy for patients with asymptomatic untreated brain metastases [16]. A recent meta-analysis assessing ICI therapy as combination therapy, ICI with radiotherapy or ICI monotherapy in patients with active melanoma brain metastases indicates that patients show better local efficacy with combination therapy and ICI plus radiotherapy than with ICI monotherapy [17].

A recent phase II trial (CONVERCE) investigated the treatment of brain metastases with cobimetinib/vemurafenib [18]. The primary endpoint of this study was intracranial response. The results of the CONVERCE study suggested that cobimetinib/vemurafenib were effective with a manageable safety profile in the melanoma population with brain metastases. Results from the primary analysis of the recent phase II TRICOTEL trial suggested that the addition of atezolizumab to cobimetinib/vemurafenib leads to beneficial intracranial activity in patients with BRAF V600 mutated melanoma with CNS metastases [19].

A randomized double-blind, pivotal phase III trial (coBRIM) compared patients on cobimetinib/vemurafenib combination therapy with vemurafenib monotherapy. OS of combination therapy was 22.3 months vs. 17.4 months and PFS was 12.3 months vs. 7.2 months, respectively, in previously untreated patients with BRAF V600 mutant advanced mM [5]. The coBRIM study did not include mM patients with brain metastases [5].

The aim of the present study was, therefore, to collect real-world data on effectiveness of cobimetinib/vemurafenib with a special focus on OS, safety and utilization of the combination therapy in two separate cohorts: patients with unresectable or metastatic BRAF V600 mutated mM without cerebral metastases and patients with metastatic BRAF V600 mutated mM with cerebral metastases. However, a comparison between the two cohorts was not planned. With coveNIS, real-world data from mM patients with brain metastases treated with the combination of cobimetinib and vemurafenib in Germany were prospectively collected and analysed, to our knowledge, for the first time.

Methods

Patients and study design

This prospective, multicentre, non-interventional post-authorisation safety study collected data on the effectiveness, safety and utilization of cobimetinib/vemurafenib in patients with mM without (Cohort A) or with cerebral metastasis (Cohort B) in routine clinical practice. The target population was adult patients with histologically confirmed unresectable or metastatic mM with a BRAF V600 mutation who received cobimetinib and vemurafenib according to the German label and summary of product characteristics (SmPC). Patients were excluded if they had hypersensitivity to any of the excipients (according to SmPC), or if they had previous treatment with BRAFi or MEKi or both prior to study entry, with the exception of retrospective inclusion (for patients receiving treatment with cobimetinib or vemurafenib or both, up to 8 weeks prior to baseline). All eligible patients who gave signed informed consent and who received at least 1 dose of cobimetinib/vemurafenib could be included.

The study started on 21 June 2017 and was completed on 30 June 2021. It was initially planned that about 30 German study sites document approximately 225 patients in the 2 cohorts (Cohort A: 157 patients without cerebral metastasis, Cohort B: 68 patients with cerebral metastasis). Patients were recruited for 31 months and followed up for a maximum of 18 months after the end of therapy. The study protocol was approved by the

ethics committee of the Ärztekammer Niedersachsen, Germany, on 24 May 2017 and the study was registered in the EU-PAS register on 10 April 2017 under the identifier EUPAS18539. This study was conducted in full conformance with the Guidelines for Good Pharmacoepidemiological Practices published by the International Society of Pharmacoepidemiology, taking into account all applicable European and German laws and regulations.

Variables

The primary effectiveness variable was OS defined as the time interval between the start of treatment (i.e. first cobimetinib or first vemurafenib treatment, whichever was later) and date of death for any cause. The secondary effectiveness variables included:

(1) PFS, defined as the interval between the study start and the date of progression as assessed by the investigator or death for any cause, whichever occurred first,
(2) Time to CNS relapse in Cohort B, defined as the interval between study start and the date of CNS relapse or death for any cause, whichever occurred first,
(3) Time to development of cerebral metastasis in Cohort A (with solely extracerebral metastases at baseline), defined as the interval between study start and the date of development of cerebral metastases, or associated date of the first concomitant local treatment for brain metastasis or death for any cause, whichever occurred first,
(4) Objective response (OR) was defined as a complete (CR) or partial remission (PR) as assessed by the investigator. Intracranial OR was defined as a CR, PR or no intracranial metastases as assessed by the investigator; extracranial OR was defined as a CR, PR or no extracranial metastases as assessed by the investigator,
(5) Utilization of cobimetinib/vemurafenib.

Safety variables included adverse events (AEs) including seriousness, severity [graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.0)] and predefined AEs of special interest (AESIs). The AESIs for the combination of vemurafenib and cobimetinib included the following: elevations in liver function tests, Grade 4; haemorrhage events, Grade ≥3 or cerebral haemorrhage of any grade; photosensitivity, Grade ≥3; QTc interval prolongation, Grade ≥3; rash, Grade ≥3; retinal vein occlusion, Grade ≥2; visual disturbance, Grade ≥3; any cutaneous primary malignancy, including squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, new primary melanoma; any non-cutaneous primary malignancy (serious AESI); cases of potential drug-induced liver injury that included an elevated alanine aminotransferase or aspartate aminotransferase in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law; and suspected transmission of an infectious agent by the study medicine.

Furthermore, for Cohort B, exploratory post-hoc subgroup analyses were performed for OS and PFS for the following subgroups: brain metastases (asymptomatic and symptomatic) and number of brain metastases (1 brain metastasis, 2–3 brain metastases and >3 brain metastases).

Data collection was based on local clinical practice; patient data were planned to be documented at baseline, every month during treatment with cobimetinib/vemurafenib, at the end of treatment, every 3 months during follow-up and at the end of the study (see Table, Supplemental digital content 1, *http://links.lww.com/MR/A341*, which shows the data collection overview).

Statistical analysis

All eligible enrolled patients were included in the analyses. Data from patients who prematurely terminated the study were used to the maximum extent possible. All effectiveness analyses were performed separately for both cohorts and all safety analyses were performed for the total population and separately for both cohorts. AEs were coded according to the Medical Dictionary for Regulatory Activities version 24.0. All statistical analyses were descriptive. Kaplan–Meier estimates were used to model data on time to event. Patients without an event were censored at the date of the last documented visit without respective event.

Results

Demography, baseline and disease characteristics

A total of 111 patients were recruited at 32 participating sites; thereof 2 patients lacked informed consent, screening failure occurred in 8 patients, off-label treatment at baseline in 5 patients and protocol deviation in 1 patient. A total of 95 patients were enrolled into the study and included in the analysis, 54 patients in Cohort A (i.e. patients without cerebral metastases) and 41 patients in Cohort B (i.e. patients with cerebral metastases). The median individual patient's study duration was 11.6 months (range: 0–30) in Cohort A and 5.5 months (range: 0–33) in Cohort B. In Cohort A, 21 (38.9%) patients completed the study while 22 (40.7%) died, and in Cohort B only 8 (19.5%) patients completed the study while 27 (65.9%) died. In both cohorts, the main reasons for the end of treatment were AEs [excluding death; Cohort A: 19 (35.2%) patients; Cohort B: 12 (29.3%) patients] and disease progression [Cohort A: 15 (27.8%) patients; Cohort B: 10 (24.4%) patients].

The median age of patients was similar in both cohorts [Cohort A: 62.5 years (range: 31–87); Cohort B: 64.0 years (range: 36–84)]. Approximately two-thirds of the patients were men (Cohort A: 63.0%, Cohort B: 63.4%). The most common Eastern Cooperative Oncology Group

performance status at baseline was 0 in Cohort A (56.3%) and 1 in Cohort B (41.7%). At baseline, the largest group of patients had elevated lactate dehydrogenase levels between >1 and ≤2× upper limit of normal both in Cohort A (42.2%) and Cohort B (54.1%).

In both cohorts, the median number of organs with extracranial metastases was 2 (Cohort A range: 1–8; Cohort B range: 0–10). In Cohort B, the median number of brain metastases was 2 (range: 1–99). A large proportion of patients in Cohort B had symptomatic brain metastases (19 patients, 46.3%). In Cohort B, the proportion of patients with 1, 2–3 or >3 brain metastases was similar (31.7%, 34.1% and 34.1%, respectively) (Table 1; see Table, Supplemental digital content 2, *http:///links.lww.com/MR/A342*, which shows additional data on demography, baseline and disease characteristics). Before the start of the study treatment, the predominant local therapies for brain metastases in Cohort B were radiotherapy (53.6%) followed by surgery (42.9%) (Table 1).

Table 1 Demography, baseline and disease characteristics

Parameter	Characteristics/ statistics	Cohort A (N = 54)	Cohort B (N = 41)
Age (years)	N	54	41
	Mean (SD)	61.9 (14.7)	62.0 (12.5)
	Median (range)	62.5 (31–87)	64.0 (36–84)
Sex	Men	34 (63.0%)	26 (63.4%)
	Women	20 (37.0%)	15 (36.6%)
ECOG PS at baseline	Number of patients with value	48 (100%)	36 (100%)
	0	27 (56.3%)	10 (27.8%)
	1	16 (33.3%)	15 (41.7%)
	2	4 (8.3%)	4 (11.1%)
	3	1 (2.1%)	6 (16.7%)
	4	-	1 (2.8%)
	5	-	-
	Missing	6 (-)	4 (-)
LDH level at baseline	Number of patients with value at visit	45 (100%)	37 (100%)
	Normal (=within range)	16 (35.6%)	12 (32.4%)
	≥1 to ≤2× ULN	19 (42.2%)	20 (54.1%)
	>2× ULN	10 (22.2%)	5 (13.5%)
	Missing	9 (-)	3 (-)
Disease stage[a]	Edition 7: IV (M1b)	4 (7.4%)	-
	Edition 7: IV (M1c)	1 (1.9%)	6 (14.6%)
	Edition 8: IIIC	6 (11.1%)	-
	Edition 8: IV (M1a(0))	5 (9.3%)	-
	Edition 8: IV (M1a(1))	8 (14.8%)	-
	Edition 8: IV (M1b(0))	6 (11.1%)	-
	Edition 8: IV (M1b(1))	1 (1.9%)	-
	Edition 8: IV (M1c(0))	13 (24.1%)	-
	Edition 8: IV (M1c(1))	10 (18.5%)	-
	Edition 8: IV (M1d(0))	-	15 (36.6%)
	Edition 8: IV (M1d(1))	-	20 (48.8%)
Number of extra-cranial metastatic organs	N	54	40
	Mean (SD)	2.4 (1.4)	2.6 (2.3)
	Median (range)	2.0 (1–8)	2.0 (0–10)
Number of prior adjuvant treatments	0	33 (61.1%)	25 (61.0%)
	1	21 (38.9%)	16 (39.0%)
Number of prior palliative treatments	0	43 (79.6%)	33 (80.5%)
	1	9 (16.7%)	5 (12.2%)
	2	1 (1.9%)	3 (7.3%)
	4	1 (1.9%)	-
Number of brain metastases	N	-	41
	Mean (sd)	-	8.0 (21.1)
	Median (range)	-	2.0 (1–99[b])
Symptomatic/ asymptomatic brain metastases	Asymptomatic	-	22 (53.7%)
	Symptomatic	-	19 (46.3%)
Number of brain metastases in categories by number	1		13 (31.7%)
	2–3		14 (34.1%)
	>3		14 (34.1%)
Leptomeningeal disease	No	-	36 (92.3%)
	Yes	-	3 (7.7%)
	Missing	-	2 (-)
Prior local treatment	Number of patients	-	28
	Radiotherapy	-	15 (53.6%)
	Surgery	-	12 (42.9%)
	Other	-	1 (3.6%)

Percentages by categories are based on the number of subjects with non-missing data.
ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.
[a]According to the American Joint Committee on Cancer, the seventh and eighth editions, cancer staging manual.
[b]The maximum of 99 brain metastases represents a high number that is not precisely known.

Exposure to cobimetinib/vemurafenib and subsequent treatment

The median treatment duration with cobimetinib was 93 days (range: 5–916) and with vemurafenib 98 days (range: 5–916) in the total population. For both cobimetinib and vemurafenib, patients in Cohort A had a longer median treatment duration than patients in Cohort B (Table 2). In the total population, the median number of days dosed was similar for cobimetinib with 90 days (range: 4–916) and vemurafenib with 91 days (range: 4–916). For both cobimetinib and vemurafenib, patients in Cohort A had more days dosed than patients in Cohort B (Table 2). In Cohort A, no dose modifications occurred and in Cohort B, 7.1% of patients had at least 1 dose modification for both cobimetinib and vemurafenib.

Half of the patients in Cohort A (50.0%) and one-third of the patients in Cohort B (34.1%) had a least 1 treatment following cobimetinib/vemurafenib. The most frequently reported antineoplastic agents in Cohort A were nivolumab (24.1%; mostly in combination with ipilimumab) and dabrafenib (22.2%; mostly in combination with trametinib), and in Cohort B ipilimumab (19.5%) and nivolumab (17.1%) (mostly as a combination of ipilimumab/nivolumab). Radiotherapy following cobimetinib/vemurafenib was reported for 5.6% of patients in Cohort A and for 17.1% patients in Cohort B.

Effectiveness outcomes

The primary endpoint, median OS, was 21.6 months [95% confidence interval (CI): 11.1–not estimable (NE)] in Cohort A and 7.4 months (95% CI: 4.1–11.5) in Cohort B (Table 2). A descriptive subgroup analysis of Cohort B according to the number of brain metastases showed a decrease in median OS from 11.5 months (95% CI: 4.8–NE) in patients with 1 brain metastasis to 4.1 months

Table 2 Exposure to cobimetinib/vemurafenib and effectiveness outcomes

	Cohort A (N = 54)	Cohort B (N = 41)
Exposure to cobimetinib/vemurafenib		
Length of time on treatment (days): cobimetinib		
Median (range)	94.5 (8–916)	83.0 (5–691)
Length of time on treatment (days): vemurafenib		
Median (range)	107.5 (8–916)	83.0 (5–691)
Number of days dosed: cobimetinib		
Median (range)	92.0 (8–916)	83.0 (4–691)
Number of days dosed: vemurafenib		
Median (range)	92.0 (8–916)	83.0 (4–691)
Primary endpoint – overall survival		
Median OS (95% CI) (months)	21.6 (11.1–NE)	7.4 (4.1–11.5)
Subgroups of Cohort B, median OS (95% CI) (months)		
1 brain metastasis		11.5 (4.8–NE)
2–3 brain metastases		6.3 (1.4–20.1)
>3 brain metastases		4.1 (1.0–10.6)
Asymptomatic brain metastases		5.7 (3.3–22.7)
Symptomatic brain metastases		7.4 (2.6–16.0)
Secondary endpoint – progression-free survival		
Median PFS (95% CI) (months)	6.9 (4.9–13.8)	5.2 (2.6–8.3)
Subgroups of Cohort B, median PFS (95% CI) (months)		
1 brain metastasis		12.3 (2.6–12.3)
2–3 brain metastases		4.2 (1.9–6.4)
>3 brain metastases		5.2 (0.5–8.3)
Asymptomatic brain metastases		6.4 (1.3–22.7)
Symptomatic brain metastases		5.2 (1.9–8.3)
Secondary endpoints		
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; PFS, progression-free survival; OS, overall survival.

(95% CI: 1.0–10.6) in patients with more than 3 brain metastases. Patients with symptomatic brain metastases had a longer median OS than patients with asymptomatic brain metastases [symptomatic: 7.4 months (95% CI: 2.6–16.0), asymptomatic 5.7 months (95% CI: 3.3–22.7)] (Table 2 and Fig. 1).

For Cohort A, the median PFS was 6.9 months (95% CI: 4.9–13.8) and the median time to development of cerebral metastases was 8.4 months (95% CI: 5.8–18.7) (Table 2). For Cohort B, the median PFS was 5.2 months (95% CI: 2.6–8.3) and the median time to CNS relapse was 4.3 months (95% CI: 2.6–5.7) (Table 2).

A descriptive subgroup analysis of Cohort B showed that patients with 1 brain metastasis had the longest median overall PFS [12.3 months (95% CI: 2.6–12.3)] and patients with 2–3 brain metastases had the shortest median PFS [4.2 months (95% CI: 1.9–6.4)]. Patients with asymptomatic brain metastases had a longer median overall PFS [6.4 months (95% CI: 1.3–22.7)] than patients with symptomatic brain metastases [5.2 months (95% CI: 1.9–8.3)] (Table 2 and Fig. 1).

The OR rate (ORR), intracranial ORR and extracranial ORR could not be estimated reliably in this study due to the proposed assessments and their suggested timings being non-mandatory in the observational plan, resulting in too few tumour assessments being reported.

Utilization of cobimetinib/vemurafenib

In both cohorts, the majority of patients had no prior adjuvant treatment (Cohort A: 61.1%; Cohort B: 61.0%) and no prior palliative treatment (Cohort A: 79.6%; Cohort B: 80.5%) (Table 3). Among patients with prior palliative treatment, 10 (18.5%) patients in Cohort A and 5 (12.2%) patients in Cohort B received anti-PD-1-based immunotherapy. After progression, within Cohort A approximately half of the patients continued to receive treatment with cobimetinib (47.8%) and vemurafenib (56.5%), and within Cohort B, 61.1% of patients continued to receive treatment with cobimetinib and with vemurafenib; data concerning treatment after progression are missing for more than half of the patients (Table 3).

Safety results

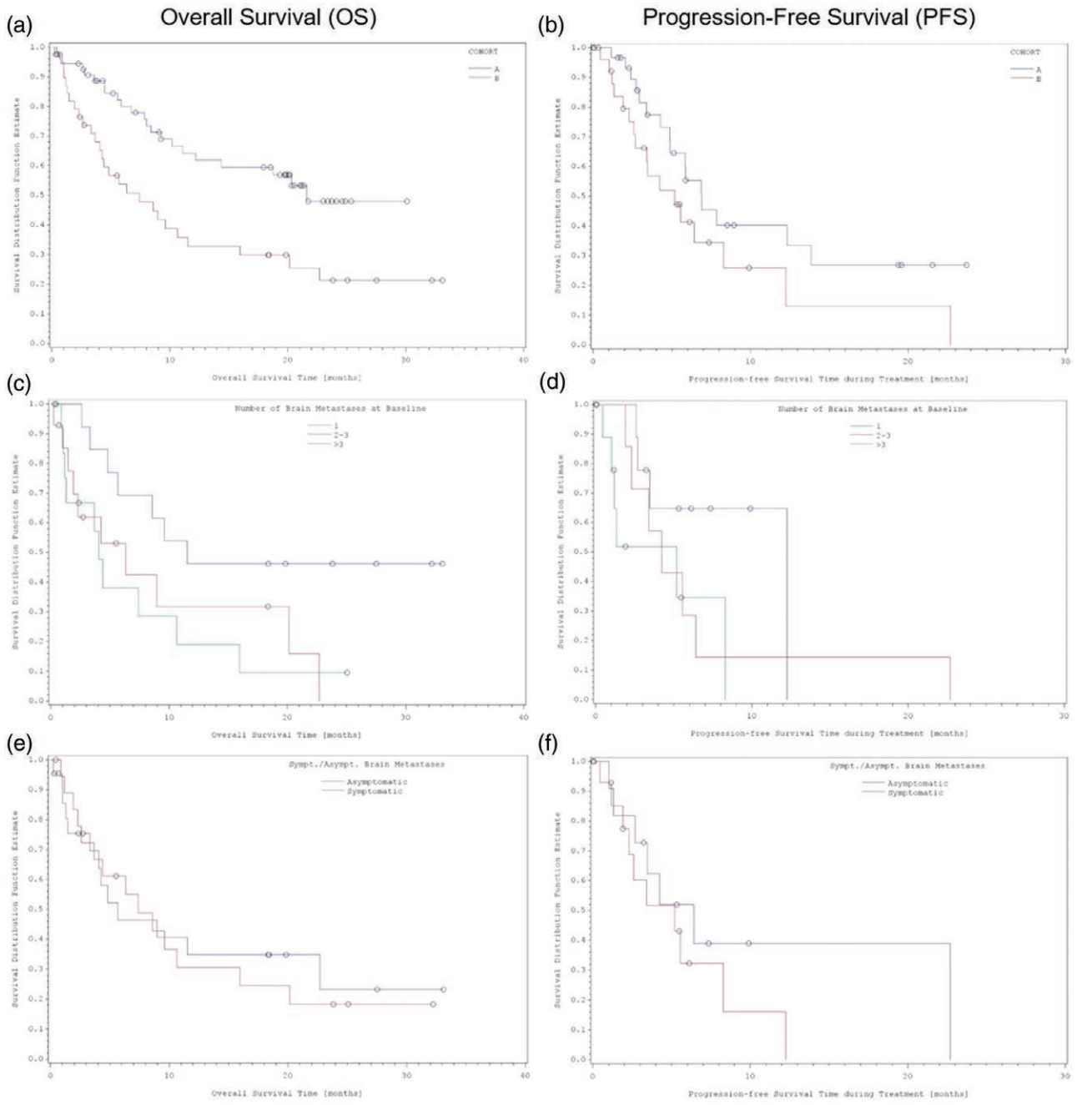
In the total analysis population, 85.3% of patients experienced an AE (Cohort A: 83.3%; Cohort B: 87.8%) and 64.2% of patients had AEs with CTCAE Grade ≥3 (Cohort A: 57.4%; Cohort B: 73.2%). The most commonly reported AEs in both cohorts by preferred term were 'diarrhoea' (36.8%), 'pyrexia' (20.0%) and 'rash' (17.9%) and the most commonly reported AEs with Grade ≥3 by preferred term were 'pyrexia' (7.4%), 'diarrhoea' (6.3%) and 'pneumonia' (6.3%) (Table 4). The most commonly reported AEs by cohort are shown in Table 4.

In the total analysis population, serious AEs were experienced by 57 (60.0%) patients [Cohort A: 28 (51.9%); Cohort B: 29 (70.7%)], adverse drug reactions (ADRs) related to cobimetinib and vemurafenib by 51 (53.7%) patients [Cohort A: 31 (57.4%); Cohort B: 20 (48.8%)], and AEs leading to treatment discontinuation by 54 (56.8%) patients [Cohort A: 30 (55.6%); Cohort B: 24 (58.5%)]. The most commonly reported serious AEs, ADRs and AEs leading to treatment discontinuation can be found in Table 4.

Some of the AEs associated with the nervous system (System Organ Class: Nervous system disorders) occurred more frequently in Cohort B. Examples of those AEs are 'headache' (Cohort A: 1.9%; Cohort B: 14.6%; see Table, Supplemental digital content 3, *http://links.lww.com/MR/A343*, which shows frequent AEs) or 'seizure', which was reported as a serious AE in no patient of Cohort A and in 7.3% of patients in Cohort B (Table 4).

There were 22 patients (23.2%) who experienced AESIs (see Methods, Variables) and the most common AESI in both cohorts was 'rash Grade ≥3' (Cohort A: 18.5%, Cohort B: 9.8%) (Table 5). 'Cutaneous primary malignancy' was experienced by 2 patients (4.9%) in Cohort B, and none of the patients in any cohort experienced any event of

Fig. 1



Overall survival (OS) and progression-free survival (PFS) in the total analysis population and in subgroups of Cohort B. Kaplan–Meier plots of OS (a, c, and e) and PFS (b, d, and f) in the total analysis population by cohort (a and b), in Cohort B by number of brain metastases at baseline (c and d; 1, 2–3 and >3 brain metastases) and in Cohort B by asymptomatic/symptomatic brain metastases (e and f).

'photosensitivity Grade ≥3' or 'QTc interval prolongation Grade ≥3'.

A total of 17 fatal AEs were reported in 13 patients, that is, for 5 patients (9.3%) in Cohort A and 8 patients (19.5%) in Cohort B (see Table, Supplemental digital content 4, *http://links.lww.com/MR/A344*, which lists fatal AEs by the patient). Of these, 5 fatal AEs in 2 patients were judged to be related to both cobimetinib and vemurafenib. These were 'sepsis' in a patient in Cohort A and 'blood creatine phosphokinase increased', 'colitis', 'renal failure' and 'rhabdomyolysis' in a patient in Cohort B (see Table, Supplemental digital content 4, *http://links.lww.com/MR/A344*).

Table 3 Utilization of cobimetinib/vemurafenib

Parameter	Characteristics	Cohort A (N = 54)	Cohort B (N = 41)
Number of adjuvant treatments	0	33 (61.1%)	25 (61.0%)
	1	21 (38.9%)	16 (39.0%)
Type of adjuvant treatment	None	33 (61.1%)	25 (61.0%)
	Clinical trial: coveNIS	1 (1.9%)	-
	Interferon	8 (14.8%)	7 (17.1%)
	Other[a]	12 (22.2%)	9 (22.0%)
Number of palliative treatments	0	43 (79.6%)	33 (80.5%)
	1	9 (16.7%)	5 (12.2%)
	2	1 (1.9%)	3 (7.3%)
	4	1 (1.9%)	-
Type of palliative treatment	None	43 (79.6%)	33 (80.5%)
	Dacarbazine	-	1 (2.4%)
	Ipilimumab and nivolumab	4 (7.4%)	5 (12.2%)
	PD-1 antibody (nivolumab)	4 (7.4%)	2 (4.9%)
	PD-1 antibody (pembrolizumab)	6 (11.1%)	3 (7.3%)
	Other	1 (1.9%)	-
Treatment with cobimetinib after progression	No	12 (52.2%)	7 (38.9%)
	Yes	11 (47.8%)	11 (61.1%)
	Missing	31 (-)	23 (-)
Treatment with vemurafenib after progression	No	10 (43.5%)	7 (38.9%)
	Yes	13 (56.5%)	11 (61.1%)
	Missing	31 (-)	23 (-)

Percentages by categories are based on the number of subjects with non-missing data.

[a]The major type of adjuvant therapy was pembrolizumab in Cohort A (5 patients) and radiotherapy in Cohort B (7 patients).

Table 4 Overview of adverse events and most frequent preferred terms

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 serious AEs		
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[a]		
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%)	

In general, the 3 most frequent preferred terms are shown for every type of AE. Exceptions to this may arise if more than one preferred term was reported for the same number of patients or if preferred terms were reported for only 1 or 2 patients.

ADR, adverse drug reaction; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

[a]Both temporary and permanent 'AEs leading to treatment discontinuation' were included.

Discussion

Strengths and limitations of the study

MM patients with brain metastases are usually excluded from clinical trials. To our knowledge, this is the first study, which prospectively collected data on cobimetinib/vemurafenib therapy in mM patients with brain metastases, therefore contributing to closing the data gap in this patient group. Overall, 32 study centres across Germany and 95 patients participated in this study. This indicates that the study population may be considered a representative population of patients with unresectable or metastatic BRAF V600 mutant mM treated with cobimetinib plus vemurafenib in Germany. Bearing in mind the limitations of the NIS setting, the initially expected total sample size of 225 enrolled patients was not achieved. In fact, only 95 patients were enrolled: 54 patients in Cohort A (35% of expected) and 41 patients in Cohort B (60% of expected). The main reason for the lower-than-planned number of patients in this study was a change in the local standard of care for mM and the approval of alternative, more effective therapies. Due to the smaller sample size, the statistical estimations were not as precise as originally planned. For the same reason, the exploratory post-hoc subgroup analyses for OS and PFS in Cohort B should be interpreted with caution. Moreover, the proposed assessments and their suggested timings in the observation plan were not mandatory due to the non-interventional design of the study, leading to some missing data.

coveNIS results in the context of other studies

The aim of this observational study was the collection of data on the effectiveness, safety and utilization of cobimetinib/vemurafenib therapy in a real-world setting and in 2 cohorts of patients with advanced mM without (Cohort A) and with (Cohort B) brain metastases. A direct comparison of the 2 cohorts was not intended by the protocol because of the imbalance between the two cohorts. Moreover, a comparison of two cohorts with the same treatment was not deemed meaningful.

Instead, Cohort A can be compared (with caution) with the cobimetinib/vemurafenib cohort (N = 247; without brain metastases) of the pivotal coBRIM trial regarding the OS data [5,20,21]. Median OS was similar between these 2 cohorts (coBRIM: 22.3 months, 95% CI: 20.3–NE; coveNIS: 21.6 months, 95% CI: 11.1–NE), thereby confirming the favourable OS results of the pivotal trial in a real-world setting.

Table 5 Adverse events of special interest

Number of Patients with AESI Type of AESI	Cohort A (N = 54)	Cohort B (N = 41)	Total (N = 95)
AESIs	11 (20.4%)	11 (26.8%)	22 (23.2%)
Any cutaneous primary malignancy[a]	0 (0.0%)	2 (4.9%)	2 (2.1%)
Elevations in liver function tests, Grade 4	1 (1.9%)	0 (0.0%)	1 (1.1%)
Haemorrhagic events, Grade ≥3, or any grade cerebral haemorrhage	2 (3.7%)	1 (2.4%)	3 (3.2%)
Potential medicine-induced liver injury[b]	1 (1.9%)	3 (7.3%)	4 (4.2%)
Rash, Grade ≥3	10 (18.5%)	4 (9.8%)	14 (14.7%)
Visual disturbance, Grade ≥3	0 (0.0%)	3 (7.3%)	3 (3.2%)
SMQ haemorrhages narrow search term	7 (13.0%)	3 (7.3%)	10 (10.5%)

AESI, adverse events of special interest; SMQ, Standardized MedDRA query.
[a]Including squamous cell carcinoma, keratoacanthoma, basal cell carcinoma and new primary melanoma.
[b]Potential medicine-induced liver injury that includes an elevated alanine transaminase (ALT) or aspartate transaminase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.

Although there were no data available for combined targeted therapy with cobimetinib/vemurafenib in patients with active brain metastases until now, Cohort B can cautiously be put into context with the following studies on targeted therapies of BRAF V600 mutated melanoma with brain metastases regarding OS:

In a phase II trial, patients with brain metastases who were either previously treated (Cohort 1 N = 90) or previously untreated (Cohort 2 N = 56), received vemurafenib until disease progression or intolerance [22]. The median OS was 8.9 months (range: 0.6–34.5) in Cohort 1 and 9.6 months (range: 0.7–34.3) in Cohort 2 [22].

In the ongoing COMBI-MB phase II trial, patients with brain metastases were treated with dabrafenib plus trametinib in 4 cohorts [23]. Median OS in an interim analysis was 10.8 months (95% CI: 8.7–19.6) in the largest cohort (Cohort A) including 76 patients with BRAF V600E-positive, asymptomatic brain metastases and without previous local brain therapy [23].

A retrospective real-world study assessed the treatment of patients with various combinations of BRAF/MEK inhibitors (N = 65; 53 patients received dabrafenib/trametinib, 10 received cobimetinib/vemurafenib, 1 received encorafenib/binimetinib, and 1 received vemurafenib/trametinib) and median OS was 9.5 months (95% CI: 7.7–13.5) [11].

In BREAK-MB, an open-label phase II trial, patients with previously untreated brain metastases (Cohort A) or progressive brain metastases after previous local treatments (Cohort B) were treated with dabrafenib [24]. Median OS was 16.3 weeks or 3.8 months (95% CI: 6.9, 22.4 weeks) in Cohort A and 21.9 weeks or 5 months (95% CI 15.3–NR, not reached in weeks) in Cohort B [24].

Overall, the median OS in Cohort B of coveNIS was 7.4 months (95% CI: 4.1–11.5), which was slightly shorter than in the phase II study with vemurafenib (Cohort 1: 8.9 months; Cohort 2: 9.6 months) [23], in the COMBI-MB trial (Cohort A: 10.8 months) [24] and in the real-world study (9.5 months) [9] and slightly longer than in the BREAK-MB study (Cohort A: 16.3 weeks or 3.8 months; Cohort B 21.9 weeks or 5 months) [24].

In Cohort B of coveNIS, the median OS negatively correlated with the number of brain metastases (1 brain metastasis, 11.5 months; 2–3 brain metastases, 6.3 months; >3 brain metastases, 4.1 months; Table 2), which is line with the results of other studies [25,26]. However, patients with symptomatic brain metastases showed higher median OS values compared to patients with asymptomatic brain metastases, which is in contrast to the published data [16,27]. Nevertheless, this exploratory post-hoc result should be interpreted with caution due to the small size of the subgroups of Cohort B (asymptomatic brain metastases, N = 22; symptomatic brain metastases, N = 19).

Collectively, the OS rates in Cohort A and Cohort B of coveNIS are in line with the OS data from other trials with BRAF/MEK inhibitors for mM.

The median time to development of cerebral metastases (Cohort A of coveNIS) was 8.4 months. In a previous study on the development of brain metastases in patients with metastatic melanoma treated with ipilimumab, 10 (21.7%) patients developed brain metastases in a median time of 6.58 months after treatment initiation [28]. Therefore, the times to event differ slightly, which may be due to the different study settings that require caution when comparing results.

Reported adverse events

All reported AEs that occurred in at least 10% of patients in any cohort or the total analysis population (see Table, Supplemental digital content 3, *http://links.lww.com/MR/A343*) are listed in the current version of the SmPCs for cobimetinib or vermurafenib or both as very common side effects [29,30]. These include 'diarrhoea', 'nausea', 'vomiting', 'pyrexia' and 'rash'. The 5 fatal AEs that were judged to be related to the study medication in 2 patients (i.e. preferred terms 'sepsis', 'colitis', 'renal failure', 'rhabdomyolysis' and 'blood creatine phosphokinase increased') not only differ on the preferred term level but also belong to different system organ classes so that no particular cluster of treatment-related fatal AEs can be identified (Table, Supplemental digital content 4, *http://links.lww.com/MR/A344*). Moreover, of the reported treatment-related fatal AEs, 'blood creatine phosphatase increased' and 'rhabdomyolysis' are the only known ADRs listed in the SmPCs of vemurafenib and cobimentib [29,30]. Regarding Cohort B, some of the

reported AEs such as 'headaches' and 'seizures', occurring more frequently in Cohort B than in Cohort A, may be attributed to the presence of cerebral metastases. Indeed, 'headaches' [31–33] and 'seizures' [20,34,35] are common in patients with cerebral metastases. Overall, the safety results in Cohort A and Cohort B of coveNIS are in line with the known safety profile of cobimetinib/vemurafenib therapy and no new safety signals were observed. In comparison to alternative target therapies, namely dabrafenib/trametinib (combiDT), pyrexia occurred less frequently under the therapy with cobimetinib/vemurafenib (coveNIS) (coveNIS 20.0% vs. combiDT 59% [36] or >70% [37]).

Conclusion

In conclusion, coveNIS provides valuable real-life insights into the cobimetinib/vemurafenib combination therapy for mM patients without and especially with cerebral metastases, who are rarely included in clinical trials. Overall, the OS rates in Cohort A and Cohort B of coveNIS are in line with the OS data from other trials with BRAF/MEK inhibitors for mM. No new safety signals were observed.

Acknowledgements

The authors would like to thank the patients, physicians and site staff who participated in this study. Anna Schuler managed the clinical study report process. Nadine Schmidt and Susanne Koch were involved in the safety data management. Pauline Gerard-Duhard reviewed the clinical study report. Editorial support in drafting the article was provided by Hanna Neymeyer and Michael Stauber of *AMS* Advanced Medical Services GmbH, with funding from Roche Pharma AG; Grenzach-Wyhlen, Germany, prior to review, revision and the decision to publish by the authors.

This study was funded by Roche Pharma AG, Grenzach-Wyhlen, Germany. Roche was involved in the design and conduct of the study; collection, management, analysis and interpretation of data; and preparation, review and approval of the article.

K.C.K, D.D., G.S., D.G., J.H., F.M., P.T., R.S., T.T., M.K. and N.-P.H. contributed to data acquisition and analysis, reviewed and approved the final version. E.M., A.Z.-S. and M.T.N contributed to the study conception or design, contributed to data analysis and interpretation, prepared the original draft, and reviewed and approved the final version. P.M. contributed to the study conception or design, contributed to data acquisition, analysis and interpretation, prepared the original draft, and reviewed and approved the final version.

Data sharing statement: Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Conflicts of interest

K.C.K. has received honoraria or consultancy honoraria from Bristol-Myers Squibb, MSD, Novartis and Sanofi-Aventis; research funding from Novartis; and travel support from Bristol-Myers Squibb, MSD, Novartis and Roche. D.D. has received consultancy and lecture honoraria or support for travel expenses / participation fees by Amgen, BMS, Kyowa Kirin, MSD, Mylan, Novartis, Pfizer, Pierre Fabre, Roche and Sanofi. G.S. has received honoraria from Bristol-Myers Squibb, Novartis, Merck Sharp & Dohme and Roche. D.G. has received consultancy honoraria as well as reimbursement for travel expenses and participation fees by Bristol-Myers Squibb, Novartis, Pierre Fabre, Immunocore, Sanofi and Sun Pharma. J.C.H. has received consultancy and lecture honoraria or support for travel expenses / participation fees by Almirall, Amgen, BMS, GSK, Immunocore, MSD, Novartis, Pierre Fabre, Roche, Sanofi and Sun Pharma. F.M. has received travel support or/and speaker's fees or/and advisor's honoraria by Novartis, Roche, BMS, MSD, Pierre Fabre and Sanofi; and research funding from Novartis and Roche. P.T. has received honoraria from Bristol-Myers Squibb, Novartis, Merck Sharp & Dohme, Pierre Fabre, CureVac, Merck Serono, Sanofi, Roche, Kyowa Kirin and Biofrontera; and travel support from Bristol-Myers Squibb and Pierre Fabre. R.S. has received honoraria from Kyowa Kirin, 4Sc, Takeda, Innate Pharma, Stemline, miRagen Therapeutics Inc., Recordati, Galderma, Hoffmann La Roche, Novartis, Abbvie, Janssen and Leo Pharma. T.T. has received lecture honoraria and travel support from BMS, MSD and Novartis. M.K. has received honoraria from Bristol-Myers Squibb, Novartis, Pierre Fabre, MSD, Sanofi, Roche and Sun Pharma. N.-P.H. has received honoraria from Bristol-Myers Squibb, Novartis, Roche, Kyowa Kirin; and travel support from Novartis and Pfizer. E.M., A.Z.-S. and M.T.N. are employees of Roche Pharma AG. P.M. has received consultancy and lecture honoraria or support for travel expenses / participation fees by Amgen, BMS, Beiersdorf, Immunocore, Merck Serono, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi Genzyme and Sun Pharma.

References

1 McCourt C, Dolan O, Gormley G. Malignant melanoma: a pictorial review. *Ulster Med J* 2014; **83**:103–110.

2 Krebs in Deutschland für 2017/2018. In: Robert Koch-Institut, die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V, Hrsg. 13. Ausgabe. 2021. https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2021/krebs_in_deutschland_2021.pdf?__blob=publicationFile. [Accessed 5 June 2023]

3 Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, *et al.*; for members of the American Joint Committee on Cancer Melanoma Expert Panel and the International Melanoma Database and Discovery

Platform. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017; **67**:472–492.
4 Lo JA, Fisher DE. The melanoma revolution: from UV carcinogenesis to a new era in therapeutics. *Science* 2014; **346**:945–949.
5 Ascierto PA, McArthur GA, Dréno B, Atkinson V, Liszkay G, Di Giacomo AM, *et al*. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2016; **17**:1248–1260.
6 Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, *et al*. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015; **373**:23–34.
7 Comito F, Pagani R, Grilli G, Sperandi F, Ardizzoni A, Melotti B. Emerging novel therapeutic approaches for treatment of advanced cutaneous melanoma. *Cancers* 2022; **14**:271.
8 Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, *et al*. Mutations of the BRAF gene in human cancer. *Nature* 2002; **417**:949–954.
9 Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* 2002; **94**:2698–2705.
10 Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the metropolitan Detroit cancer surveillance system. *J Clin Oncol* 2004; **22**:2865–2872.
11 Drago JZ, Lawrence D, Livingstone E, Zimmer L, Chen T, Giobbie-Hurder A, *et al*. Clinical experience with combination BRAF/MEK inhibitors for melanoma with brain metastases: a real-life multicenter study. *Melanoma Res* 2019; **29**:65–69.
12 Dummer R, Goldinger SM, Turtschi CP, Eggmann NB, Michielin O, Mitchell L, *et al*. Vemurafenib in patients with BRAF(V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. *Eur J Cancer* 2014; **50**:611–621.
13 Larkin J, Del Vecchio M, Ascierto PA, Krajsova I, Schachter J, Neyns B, *et al*. Vemurafenib in patients with BRAF(V600) mutated metastatic melanoma: an open-label, multicentre, safety study. *Lancet Oncol* 2014; **15**:436–444.
14 Kefford RF, Maio M, Arance A, Nathan P, Blank C, Avril MF. An open-label, single-arm, phase 2, multicenter study. *Pigment Cell Melanoma Res* 2013; **26**:932–1019.
15 Yushak ML, Chiang VL, Kluger HM. Clinical trials in melanoma patients with brain metastases. *Pigment Cell Melanoma Res* 2015; **28**:741–743.
16 Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, *et al*. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol* 2018; **19**:672–681.
17 Kim PH, Suh CH, Kim HS, Kim KW, Kim DY, Lee EQ, *et al*. Immune checkpoint inhibitor with or without radiotherapy in melanoma patients with brain metastases: a systematic review and meta-analysis. *Korean J Radiol* 2021; **22**:584–595.
18 CONVERCE. Vemurafenib and cobimetinib combination in BRAF mutated melanoma with brain metastasis (CONVERCE). https://clinicaltrials.gov/ct2/show/NCT02537600. [Accessed 19 April 2023]
19 Dummer R, Queirolo P, Abajo Guijarro AM, Hu Y, Wang D, de Azevedo SJ, *et al*. Atezolizumab, vemurafenib, and cobimetinib in patients with melanoma with CNS metastases (TRICOTEL): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol* 2022; **23**:1145–1155.
20 Posner JB. Brain metastases: 1995. A brief review. *J Neurooncol* 1996; **27**:287–293.
21 Dréno B, Ribas A, Larkin J, Ascierto PA, Hauschild A, Thomas L, *et al*. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. *Ann Oncol* 2017; **28**:1137–1144.
22 McArthur GA, Maio M, Arance A, Nathan P, Blank C, Avril MF, *et al*. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study. *Ann Oncol* 2017; **28**:634–641.
23 Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, Arance A, *et al*. Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol* 2017; **18**:863–873.
24 Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, *et al*. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; **13**:1087–1095.
25 Davies MA, Liu P, McIntyre S, Kim KB, Papadopoulos N, Hwu WJ, *et al*. Prognostic factors for survival in melanoma patients with brain metastases. *Cancer* 2011; **117**:1687–1696.
26 Bander ED, Yuan M, Carnevale JA, Reiner AS, Panageas KS, Postow MA, *et al*. Melanoma brain metastasis presentation, treatment, and outcomes in the age of targeted and immunotherapies. *Cancer* 2021; **127**:2062–2073.
27 Raizer JJ, Hwu WJ, Panageas KS, Wilton A, Baldwin DE, Bailey E, *et al*. Brain and leptomeningeal metastases from cutaneous melanoma: survival outcomes based on clinical features. *Neuro Oncol* 2008; **10**:199–207.
28 Frenard C, Peuvrel L, Jean MS, Brocard A, Knol AC, Nguyen JM, *et al*. Development of brain metastases in patients with metastatic melanoma while receiving ipilimumab. *J Neurooncol* 2016; **126**:355–360.
29 SmPC. Summary of product characteristics SmPC cobimetinib (cotellic). https://www.ema.europa.eu/en/documents/product-information/cotellic-epar-product-information_en.pdf. [Accessed 19 April 2023].
30 SmPC. Summary of procut characteristics SmPC for vemurafenib (zelboraf). https://www.ema.europa.eu/en/documents/product-information/zelboraf-epar-product-information_en.pdf. [Accessed 19 April 2023]
31 Forsyth PA, Posner JB. Headaches in patients with brain tumors: a study of 111 patients. *Neurology* 1993; **43**:1678–1683.
32 Suwanwela N, Phanthumchinda K, Kaoropthum S. Headache in brain tumor: a cross-sectional study. *Headache* 1994; **34**:435–438.
33 Christiaans MH, Kelder JC, Arnoldus EP, Tijssen CC. Prediction of intracranial metastases in cancer patients with headache. *Cancer* 2002; **94**:2063–2068.
34 Ajinkya S, Fox J, Houston P, Greenblatt A, Lekoubou A, Lindhorst S, *et al*. Seizures in patients with metastatic brain tumors: prevalence, clinical characteristics, and features on EEG. *J Clin Neurophysiol* 2021; **38**:143–148.
35 Argyriou AA, Chroni E, Polychronopoulos P, Argyriou K, Papapetropoulos S, Corcondilas M, *et al*. Headache characteristics and brain metastases prediction in cancer patients. *Eur J Cancer Care (Engl)* 2006; **15**:90–95.
36 Menzies AM, Ashworth MT, Swann S, Kefford RF, Flaherty K, Weber J, *et al*. Characteristics of pyrexia in BRAFV600E/K metastatic melanoma patients treated with combined dabrafenib and trametinib in a phase I/II clinical trial. *Ann Oncol* 2015; **26**:415–421.
37 Lee CI, Menzies AM, Haydu LE, Azer M, Clements A, Kefford RF, *et al*. Features and management of pyrexia with combined dabrafenib and trametinib in metastatic melanoma. *Melanoma Res* 2014; **24**:468–474.