SYNOPSIS CLINICAL STUDY REPORT

according to ICH E3 guideline

Version 1.0F, 24.04.2024

AN OPEN-LABEL PHASE II MULTICENTER STUDY OF VEMURAFENIB (ZELBORAF®) PLUS COBIMETINIB (COTELLIC®) AFTER RADIOSURGERY IN PATIENTS WITH ACTIVE BRAF-V600-MUTANT MELANOMA BRAIN METASTASES

RADIOCOBRIM STUDY

Trial Protocol version 2.0F, 20.10.2017 including amendment 01 version 3.0F, 11.12.2018

Sponsor	**Dresden University of Technology** Mommsenstraße 11, 01069 Dresden, Germany
Principal Coordinating Investigator	**Prof. Dr. med. Friedegund Meier** University Hospital Carl Gustav Carus Dresden and Carl Gustav Carus Faculty of Medicine, TUD (Dresden University of Technology) Department of Dermatology Skin Cancer Center at the University Cancer Center and National Center for Tumor Diseases Fetscherstraße 74, 01307 Dresden, Germany
Sponsor Code:	TUD-CoBRIM-067
EudraCT-Number:	2017-000768-13
ClinicalTrials.gov Identifier:	NCT03430947
Name of Finished Product and Active Substance	Finished Product: Zelboraf Active Substance: Vemurafenib Finished Product: Cotellic Active Substance: Cobimetinib

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1 SUMMARY OF TRIAL INFORMATION

Sponsor	**Dresden University of Technology** **(Technische Universität Dresden,** 01069 Dresden)
Principal Coordinating Investigator	**Prof. Dr. med. Friedegund Meier**
Full Title	An open-label phase II multicenter study of vemurafenib (Zelboraf®) plus cobimetinib (Cotellic®) after radiosurgery in patients with active BRAF-V600-mutant melanoma brain metastases
Short Title	RadioCoBRIM
Trial Protocol	Trial Protocol version 2.0 F, 20.10.2017 including amendment 01 version 3.0 F, 11.12.2018
Indication	Active BRAF-V600-mutant melanoma brain metastases
Phase of development	II
Study design	Single arm open-label multicenter study
Objective(s) of the clinical trial	Primary objective(s): To evaluate efficacy of vemurafenib plus cobimetinib after radiosurgery through determination of intracranial best overall response rate (BORR) within two years. Secondary objectives: To evaluate • Extracranial BORR • BORR calculated for the whole body tumor sites • Intracranial duration of response • Extracranial duration of response • Progression-free survival (PFS) • Overall survival (OS) • Safety • Quality of Life
Endpoints of the clinical trial	Primary Endpoint(s): BORR in the brain within two years, defined as the rate of patients with complete response (CR) or partial response (PR) assessed by modified version of RECIST 1.1 Secondary Endpoints: Efficacy • Extracranial BORR • BORR calculated for the whole body tumor sites • Intracranial duration of response • Extracranial duration of response • Progression-free survival (PFS) • Overall survival (OS) Safety • Total adverse events • Serious adverse events • ≥ Grade 3 adverse events • Adverse events of special interest

	• Adverse events leading to treatment discontinuation Quality of Life • Functional Assessment of Cancer Therapy-Brain questionnaire (FACT-Br)
Number of patients	planned sample size: 32 patients screened: 50 patients enrolled: 21 patients analysed: 20
Studied period	First patient in: 04.07.2018 Last patient in: 20.01.2021 Last patient last visit: 10.02.2023
Inclusion criteria	• Signed informed consent • Female and male patients ≥ 18 years of age • Histologically confirmed metastatic melanoma (stage IV, per AJCC staging) carrying BRAF V600-mutation • Performed SRS 14 ±7 days before baseline using a harmonized protocol in patients with at least one measurable intracranial target lesion for which the following criteria are met: • Previously untreated (Lesions in previously irradiated area should not be selected) • Largest diameter of ≥ 0.5 but ≤ 4 cm as determined by contrast-enhanced MRI and • ≤ 10 brain metastases • ECOG performance status 0 - 2 • Life expectancy ≥ 12 weeks • Adequate bone marrow function as indicated by the following: • ANC ≥ 1500/µL, • Platelets ≥ 100,000/µL and • Hemoglobin ≥ 9 g/dL • Adequate renal function, as indicated by creatinine ≤ 1.5 x ULN • Adequate liver function, as indicated by bilirubin < 1.5 x ULN and AST and ALT < 3 x ULN (documented liver metastases: AST and ALT < 5 x ULN) • Adequate coagulation within 28 days prior to baseline visit • Patients without therapeutic anticoagulation: INR or aPTT ≤ 1.5 x ULN • Patients receiving therapeutic anticoagulation: stable anticoagulation regimen and stable INR • Able to swallow pills
Exclusion criteria	• Symptomatic brain metastases requiring immediate local interventions such as neurosurgery or radiosurgery • Leptomeningeal disease (also synchronous with brain metastases) • Prior therapy with BRAF or MEK inhibitors within 12 weeks prior to baseline visit (prior therapies for metastatic melanoma including chemo-, cytokine-, immuno-, biological and vaccine-therapy are allowed) A period of at least 6 weeks must be observed between the last dose of ipilimumab and the first administration of the study treatments. Prior treatment with anti-programmed cell death (PD)-1 or anti-PD ligand 1 (PD-L1) is allowed. • Prior whole brain irradiation (Patients with prior local therapy of brain metastases are eligible)

	• Patients receiving therapeutic steroids who are not stable on corticosteroids 2 weeks before SRS
	• Active and uncontrolled infection
	• Known HIV infection or active HBV or HCV infection
	  • Active HBV infection (chronic and acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening (past or resolved HBV infections, defined as negative HBsAg test and a positive total hepatitis B core antibody test at screening, are eligible)
	  • Active HCV infection, defined as positive HCV antibody test and positive HCV RNA test at screening
	• Intracranial radiation therapy within 14 days prior to SRS
	• Extracranial radiation therapy within the last 14 days prior to baseline visit
	• Treatment with strong CYP3A4/5 inhibitors (e.g. ketoconazole) and inducers (e.g. phenytoin, carbamazepine). (anticonvulsant levetiracetam is allowed; patient should be stable on levetiracetam for 2 weeks)
	• Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI v4.0) [NCI, 2009] Grade 2 or higher from previous anti-cancer therapy, except alopecia.
	• Conditions that will interfere significantly with the absorption of drugs (e.g. Colitis ulcerosa)
	• Inability to undergo MRI secondary to:
	  • Metal,
	  • Claustrophobia, or
	  • Gadolinium contrast allergy
	• Previous malignancies active within the last 3 years, with the exception of locally curable cancers that have been treated to complete remission or untreated stage I chronic lymphoid leukemia.
	• Unwillingness or inability to comply with study and follow-up procedures
	• Known hypersensitivity to any of the excipients of cobimetinib and vemurafenib
	• The following foods/supplements are prohibited at least 7 days prior to initiation of and during study treatment:
	  • St. John’s wort or hyperforin (potent cytochrome P450 CYP3A4 enzyme inducer)
	  • Grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor)
	• Patient is included in another interventional trial
	• Use of any investigational or non-registered product within 4 weeks prior to baseline visit
	• Woman of childbearing age with the exception they meet at least one of the following criteria:
	  • Post-menopausal,
	  • Sterilization,
	  • Consistently & correct application of contraceptives (Pearl Index < 1%),
	  • sexual abstinence, or
	  • vasectomy of the partner
	• Pregnant or lactating women
	• History, risk factor or retinal pathology that increases the risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR): evidence

	of retinal pathology that is considered a risk factor for RVO or CSR, or a history of retinal detachment, central serous chorioretinopathy or retinal vein thrombosis. The risk factors for RVO are listed below: • Uncontrolled glaucoma with intraocular pressures > 21 mm Hg, • Serum cholesterol ≥ Grade 2 (≥ 7.75 mmol/L), • Hypertriglyceridemia ≥ Grade 2 (≥ 3.42 mmol/L), • Hyperglycemia (fasting) ≥ Grade 2 (≥ 8.9 mmol/L). • History of clinically significant cardiac dysfunction including: • Myocardial infarction, • Severe/unstable angina pectoris, • Symptomatic congestive heart failure (NYHA stage ≥ 2), • cerebrovascular accident or transient ischemic attack within the previous 6 months, • History of congenital long QT syndrome or mean QTcF > 450 msec or uncorrectable electrolyte abnormalities, • Hypertension > Grade 2 not controlled by medications • Left ventricular ejection fraction (LVEF) < 50%, or • Uncontrolled arrhythmias	
Test product(s)	**Cobimetinib** Dose of administration: 60 mg once a day (OD) Mode of administration: per os Batch number(s): 1154907, 1155758, 1160071, 1163640, 1173739	**Vemurafenib** Dose of administration: 960 mg twice a day (BID) Mode of administration: per os Batch number(s): 1154740, 1155763, 1163639, 1173726
Duration of treatment	Product: Cobimetinib Dose: 60 mg/d per os Duration: day 1-21 of each treatment cycle (max. 24 cycles) Product: Vemurafenib Dose: 960 mg twice a day per os Duration: day 1-28 of each treatment cycle (max. 24 cycles)	

2 INDIVIDUAL STUDY TABLE

Not applicable.

3 INVESTIGATORS AND TRIAL SITES

No. of Trial Site	Trial Site	Principal Investigator(s)
01	University Hospital Carl Gustav Carus Dresden and Carl Gustav Carus Faculty of Medicine, TUD (Dresden University of Technology) Department of Dermatology Fetscherstraße 74 01307 Dresden	Prof. Dr. med. Friedegund Meier
02	Department of Dermatology and National Center for Tumor Diseases University Hospital Heidelberg Im Neuenheimer Feld 440 69120 Heidelberg	Prof. Dr. med. Jessica Hassel
03	Center for Dermatooncology Department of Dermatology Eberhard Karls University of Tuebingen Liebermeisterstr. 25 72076 Tuebingen	Prof. Dr. Thomas Eigentler until 05/2021 Dr. med. Ioannis Thomas since 06/2021

4 METHODOLOGY

The RadioCoBrim study was a single-arm (uncontrolled), open label, multicenter clinical trial. Due to the nature of the trial, neither randomisation nor blinding was performed.

All patients were treated with vemurafenib and cobimetinib (schedule see Figure 1: Study schedule) for a maximum of 24 cycles. Dose changes, interruptions, and delays of vemurafenib and/or cobimetinib study treatment should have been made according to the SmPC.

Intracranial involvements and response (according to modified RECIST 1.1) were centrally assessed by a neuroradiologist from the Institute of Neuroradiology, University Hospital Carl Gustav Carus Dresden and Carl Gustav Carus Faculty of Medicine, Dresden University of Technology at baseline and every 6 weeks thereafter, using gadolinium contrast-enhanced magnetic resonance imaging (MRI). The primary endpoint (BORR according to modified RECIST 1.1) was then derived.

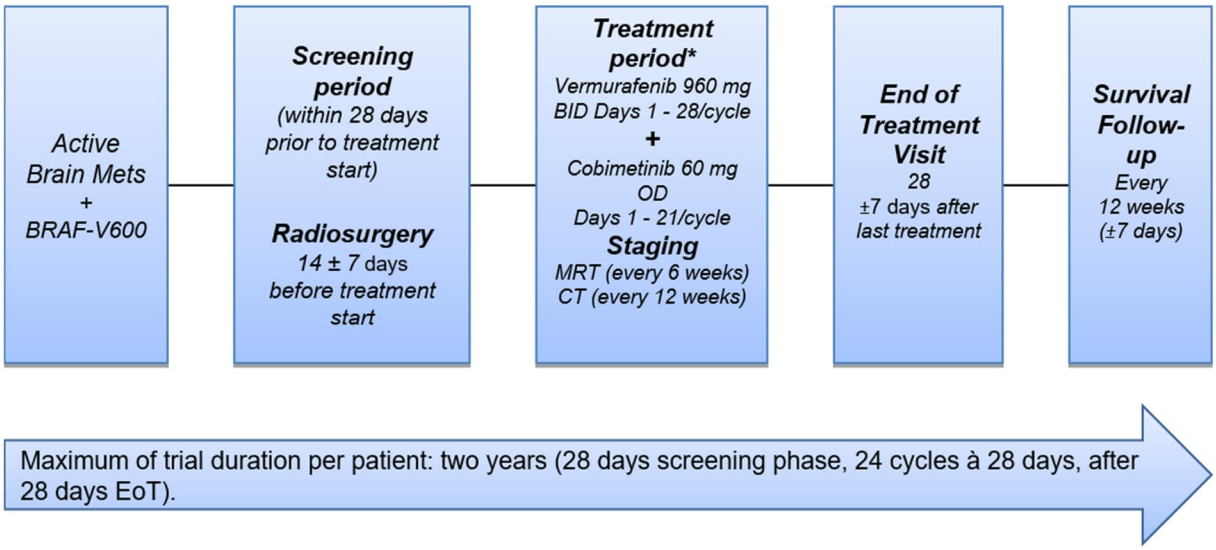

Figure 1: Study schedule

Onsite monitoring took place depending on the number of patients enrolled at each trial site on a regular basis.

No interim analysis of efficacy was planned or carried out.

One interim analysis of safety was planned and performed 3 months after the 6th patient had been enrolled. The DSMB reviewed data on all adverse events. In case of evidence suggesting a lack of safety (e.g. radionecrosis or cerebral hemorrhage in >2 patients) the DSMB was asked to provide the sponsor with recommendations regarding trial continuation, modification or termination. The DSMB meeting took place on 11th March 2019. No safety concerns were observed and the study continued without modification.

5 STATISTICAL METHODS

The final analysis was planned in detail in the statistical analysis plan (version 1.0F as of 17th November 2023). Here, only the most important specifications are presented.

The study was planned with a significance level of 5 percent and a power of 90 percent was aimed at. No interim analysis of efficacy was planned. In the confirmatory analysis, one statistical test was performed in one analysis population, namely ITT population. Thus, no type-one-error adjustment was required.

Study Populations:

- Intent-to-treat population (ITT) consists of all included patients who received at least one dose of study treatment.
- Per-protocol set (PPS) consists of all patients of the ITT population without any severe protocol deviation.
- Safety analysis set consists of all subjects who received at least one dose of study treatment. Thus, in this trial, safety analysis set and ITT population are identical.

Confirmatory analysis of primary endpoint (ITT), i.e. number of patients with CR or PR as intracranial BOR acc. to modified version of RECIST 1.1 among all patients treated:

- absolute and relative frequency of patients
- exact 95 % confidence limits (Clopper-Pearson)
- two-sided exact test for single proportion with $p_0 = 0.35$ as null hypothesis proportion

The number of patients with CR or PR is divided by all patients treated with study medication. That means, cases of unknown or non-evaluable response are included in the confirmatory analysis and counted as non-CR / non-PR, hence failure.

Sensitivity analyses of primary endpoint (ITT, PPS):

i. per protocol analysis of primary endpoint analogous to ITT analysis
ii. number of patients with CR, PR, or SD as intracranial BOR acc. to RECIST 1.1: frequency and calculation of exact 95% CI
iii. number of patients with CR, or PR as intracranial BOR acc. RANO: frequency and calculation of exact 95% CI
iv. number of patients with CR, PR, or SD as intracranial BORR acc. RANO: frequency and calculation of exact 95% CI

No exact test for single proportion is performed for ii. to iv. as no null hypothesis proportion was prespecified for these sensitivity analyses.

Secondary endpoints (ITT, PPS) of efficacy:

- number of patients with CR, or PR as extracranial BOR acc. RECIST 1.1: frequency and calculation of exact 95% CI
- number of patients with CR, PR, or SD as extracranial BOR acc. RECIST 1.1: frequency and calculation of exact 95% CI
- number of patients with CR, or PR as BOR for whole body tumor sites acc. RECIST 1.1: frequency and calculation of exact 95% CI
- number of patients with CR, PR, or SD as BOR for whole body tumor sites acc. RECIST 1.1: frequency and calculation of exact 95% CI

No exact test for single proportion was performed for above mentioned secondary endpoints as no null hypothesis proportion was prespecified.

- intracranial duration of response: restricted to patients with CR or PR; PD or death counted as event, Kaplan meier methods
- extracranial duration of response: restricted to patients with CR or PR; PD or death counted as event, Kaplan meier methods
- progression free survival: PD or death counted as event, Kaplan meier methods
- intracranial progression free survival: intracranial PD or death counted as event, Kaplan meier methods
- extracranial progression free survival: intracranial PD or death counted as event, Kaplan meier methods
- overall survival: death counted as event, Kaplan meier methods

Secondary endpoint - Quality of Life (ITT, PPS):

- FACT-Br (Thavarajah et al. (2014)): mixed models with patient as random factor

Secondary endpoints of safety (ITT): frequency of adverse events, frequency of patients concerned along with 95% exact confidence interval (Clopper-Pearson) for single proportion

Due to the small numer of patients, no investigations of center effects and no subgroup analyses were prespecified. In addition, the impact of covariates on endpoints needs to be interpreted with caution. According to SAP, the role of pre-treatment with immunotherapy, initial tumor burden, and elevated LDH at study inclusion was investigated by logistic regression or Cox regression.

6 RESULTS

Patients were recruited from July 4th, 2018 to January 20th, 2021. 50 patients were screened in 3 trial sites. Among these, 20 patients were eligible and treated in this study.

Originally, a sample size of 32 patients was planned. Due to the slow recruitement rate the sponsor and the coordinating principal investigator decided to terminate study recruitement prematurely. With the sample size of 20 patients a power of 80 percent was reached for the confirmatory analysis instead of originally planned 90 percent.

6.1 CONSORT FLOW DIAGRAM

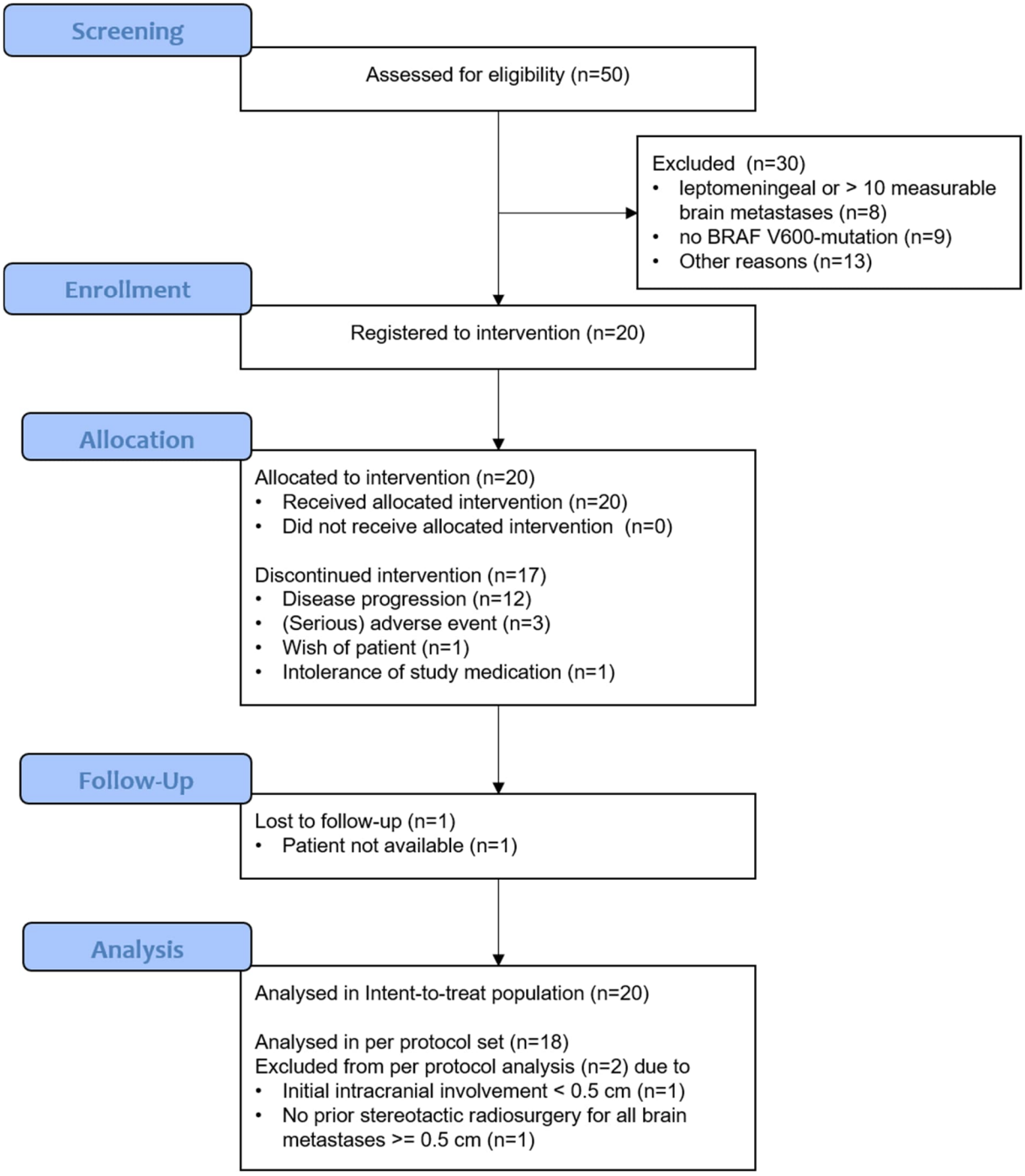

Figure 2: CONSORT Flow Diagram

6.2 ANALYSIS POPULATIONS

Intent to treat population comprises 20 patients. All of them were analysed for primary and secondary endpoints. Two patients with severe protocol deviations were excluded from per protocol set (for reasons see consort flow diagram above).

6.3 BASELINE CHARACTERISTICS

20 patients were included with a median age of 57 years. Sex was equally distributed among these patients.

In the following table, data are presented as absolute and relative frequency, or median and interquartile range.

Baseline Charactristics		ITT (N = 20)
Age at inclusion (yr)		57 [50 - 62]
Sex	male	10 (50%)
	female	10 (50%)
ECOG performance status	0	13 (65%)
	1	7 (35%)
	>= 2	0 (0%)
Increased LDH at inclusion		9 (45%)
Tumor stage (AJCC 2010)	IV	20 (100%)
Number of intracranial metastases (target and non-target)		2 [1 - 5]
Intracranial RECIST 1.1 target lesion	number of lesions	1 [1 - 3]
	sum of diameters (cm)	1.4 [0.7 - 2.9]
Intracranial RECIST 1.1 non-target lesion	number of lesions	1 [0 - 3]
Presence of extracranial metastases (target or non-target)		17 (85%)
$BRAF^{V600}$ mutation	$BRAF^{V600E}$	14 (70%)
	$BRAF^{V600K}$	4 (20%)
	$BRAF^{V600R}$	2 (10%)
Prior therapy of brain metastases	Stereotactic radiosurgery	20 (100%)
	Whole brain radiation	0 (0%)
	Systemic therapy	13 (65%)
Administration of steroides	at start of study treatment	1 (5%)
	up to 21 days before start of study treatment	3 (15%)

6.4 STUDY TREATMENT AND COMPLIANCE

All 20 patients received investigational medicinal product. The median duration of trial treatment was 7 cycles (IQR 3 to 18 cycles) for vemurafenib as well as cobimetinib. No severe

protocol deviation regarding interruption or withdrawal of IMP was observed. As well, no protocol deviation regarding administration of forbidden concomitant mediaction occured.

Reasons for early study treatment are presented in consort flow diagram, see chapter 6.1.

6.5 PRIMARY ENDPOINT – INTRACRANIAL BEST OVERALL RESPONSE

6.5.1 INTRACRANIAL BEST OVERALL RESPONSE ACC. RECIST 1.1 (**CONFIRMATORY ANALYSIS**)

Intracranial best overall response was assessed according to modified RECIST 1.1 (Eisenhauer et al. (2009)).

Modifications to RECIST 1.1 concerned the number and the minimal size of the intracranial target lesions selected at baseline. RECIST 1.1 allows the use of only 5 target lesions overall, with only 2 allowed per organ. For the purposes of this protocol, intracranial disease was measured using up to 5 intracranial target lesions. Target lesions were lesions that could be measured accurately in at least one dimension with the longest diameter ≥ 5 mm when evaluated with contrast-enhanced MRI.

Intent-to-treat Population

Intracranial BOR acc. RECIST 1.1	**ITT (n=20)**
Complete response (CR)	4 (20.0%)
Partial response (PR)	9 (45.0%)
Stable disease (SD)	2 (10.0%)
Progressive disease (PD)	4 (20.0%)
Not evaluable (NE)	1 (5.0%)

Complete or partial response was reached as BOR within two years in 13 of 20 patients (65%; 95% CI [40.8%; 84.6%]). The p-value of two-sided exact test for single proportion with null hypothesis proportion p_0=0.35 is 0.012.

Thus, in the confirmatory analysis best overall response rate acc. RECIST 1.1 of intracranial lesions is statistically significantly higher than 35 percent.

Per Protocol Set

Intracranial BOR acc. RECIST 1.1	PPS (n=18)
Complete response (CR)	3 (16.7%)
Partial response (PR)	9 (50.0%)
Stable disease (SD)	2 (11.1%)
Progressive disease (PD)	3 (16.7%)
Not evaluable (NE)	1 (5.6%)

Complete or partial response was reached as BOR within two years in 12 of 18 patients (66.7%; 95% CI [41.0%; 86.7%]). The p-value of two-sided exact test for single proportion (null hypothesis proportion p_0=0.35) is 0.012.

Hence, results in per protocol set are consistent with intent-to-treat analysis.

6.5.2 INTRACRANIAL BEST OVERALL RESPONSE RATE ACC. RECIST 1.1 INCL. SD (SENSITIVITY ANALYSIS)

In this sensitivity analysis, stable disease as best overall response within 2 years is counted as success (in addition to CR and PR).

Population	Frequency	95% exact CI
Intent-to-treat Population	15 / 20 (75.0%)	[50.9%; 91.3%]
Per Protocol Set	14 / 18 (77.8%)	[52.4%; 93.6%]

6.5.3 INTRACRANIAL BEST OVERALL RESPONSE ACC. RANO (SENSITIVITY ANALYSIS)

In this sensitivity analysis, intracranial best overall response was assessed according to RANO (Lin et al. (2015)).

Intent-to-treat Population

Intracranial BOR acc. RANO	ITT (n=20)
Complete response (CR)	4 (20.0%)
Partial response (PR)	3 (15.0%)
Stable disease (SD)	7 (35.0%)
Progressive disease (PD)	4 (20.0%)

Intracranial BOR acc. RANO	ITT (n=20)
Not evaluable (NE)	2 (10.0%)

Complete or partial response was reached as BOR within two years in 7 of 20 patients (35%; 95% exact CI [15.4%; 59.2%]).

Per Protocol Set

Intracranial BOR acc. RANO	PPS (n=18)
Complete response (CR)	3 (16.7%)
Partial response (PR)	3 (16.7%)
Stable disease (SD)	7 (38.9%)
Progressive disease (PD)	3 (16.7%)
Not evaluable (NE)	2 (11.1%)

Complete or partial response was reached as BOR within two years in 6 of 18 patients (33.3%; 95% CI [13.3%; 59.0%]).

6.5.4 INTRACRANIAL BEST OVERALL RESPONSE RATE INCL. SD ACC. RANO (SENSITIVITY ANALYSIS)

In this sensitivity analysis, stable disease as best overall response within 2 years acc. RANO is counted as success (in addition to CR and PR).

Population	Frequency	95% exact CI
Intent-to-treat Population	14 / 20 (70.0%)	[45.7%; 88.1%]
Per Protocol Set	13 / 18 (72.2%)	[46.5%; 90.3%]

6.6 SECONDARY ENDPOINTS OF EFFICACY

6.6.1 EXTRACRANIAL BOR ACC. RECIST 1.1

In the ITT population, 17 of 20 patients had extracranial involvement at inclusion (PPS: 15 of 18 patients). None of the remaining 3 patients developed extracranial lesions during the study. Otherwise, they would have been counted as progressive disease.

One patient prematurely terminated study participation before first re-staging of extracranial involvements.

Intent-to-treat Population

Extracranial BOR acc. RECIST 1.1	ITT (n=17)
Complete response (CR)	1 (5.9%)
Partial response (PR)	5 (29.4%)
Stable disease (SD)	9 (52.9%)
Progressive disease (PD)	1 (5.9%)
Not evaluable (NE)	0 (0.0%)
No imaging after start of study treatment	1 (5.9%)

Best Overall Response	Frequency	95% exact CI
CR or PR	6 / 17 (35.3%)	[14.2%; 61.7%]
CR, PR, or SD	15 / 17 (88.2%)	[63.6%; 98.5%]

Per Protocol Set

Extracranial BOR acc. RECIST 1.1	PPS (n=15)
Complete response (CR)	1 (6.7%)
Partial response (PR)	4 (26.7%)
Stable disease (SD)	8 (53.3%)
Progressive disease (PD)	1 (6.7%)
Not evaluable (NE)	0 (0.0%)
No imaging after start of study treatment	1 (6.7%)

Best Overall Response	Frequency	95% exact CI
CR or PR	5 / 15 (33.3%)	[11.8%; 61.6%]
CR, PR, or SD	13 / 15 (86.7%)	[59.5%; 98.3%]

No exact test for single proportion was performed as no null hypothesis proportion was prespecified for extracranial BOR rate.

6.6.2 WHOLE BODY TUMOR SITES BOR

BOR for whole body tumor sites was derived from intracranial and extracranial response measured by (modified) RECIST 1.1. For details, see statistical analysis plan.

No exact test for single proportion was performed as no null hypothesis proportion was prespecified for whole body BOR rate.

Intent-to-treat Population

Whole body BOR acc. RECIST 1.1	ITT (n=20)
Complete response (CR)	2 (10.0%)
Partial response (PR)	6 (30.0%)
Stable disease (SD)	1 (5.0%)
Progressive disease (PD)	8 (40.0%)
Not evaluable (NE)	1 (5.0%)
No simultaneous examination	2 (10.0%)

Best Overall Response	Frequency	95% exact CI
CR or PR	8 / 20 (40.0%)	[19.1%; 64.0%]
CR, PR, or SD	9 / 20 (45.0%)	[23.1%; 68.5%]

Per Protocol Set

Extracranial BOR acc. RECIST 1.1	PPS (n=18)
Complete response (CR)	2 (11.1%)
Partial response (PR)	5 (27.8%)
Stable disease (SD)	1 (5.6%)
Progressive disease (PD)	7 (38.9%)
Not evaluable (NE)	1 (5.6%)
No simultaneous examination	2 (11.1%)

Best Overall Response	Frequency	95% exact CI
CR or PR	7 / 18 (38.9%)	[17.3%; 64.3%]
CR, PR, or SD	8 / 18 (44.4%)	[21.5%; 69.3%]

6.6.3 INTRACRANIAL DURATION OF RESPONSE ACC. RECIST 1.1

The analysis is restricted to patients with CR or PR as intracranial BOR according to RECIST 1.1.

Intent-to-treat Population

13 patients were analysed including 9 having an event (69.2%; 7 PD and 2 deaths) and 4 being censored (30.7%).

Estimates for duration of response		
Quartile	**Estimate**	**95% CI**
Lower	1.4 months	[1.3 months; 3.6 months)
Median	3.8 months	[1.4 months; not estimable)
Upper	not estimable	[3.6; not estimable)

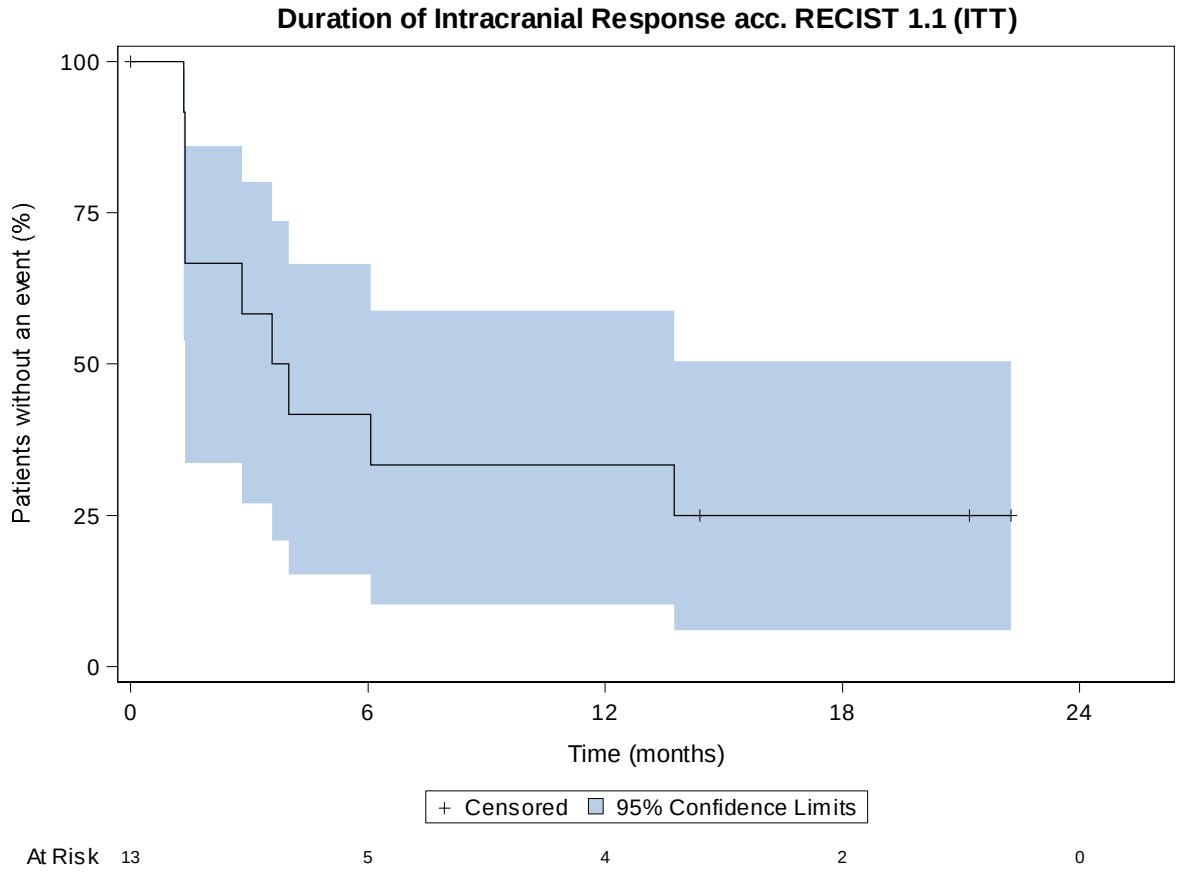

Figure 3: Kaplan Meier Plot Duration of Intracranial Response acc. RECIST 1.1 in ITT population

Per Protocol Set

12 patients analysed (8 events, 4 censored). Median duration of response 4.0 months (95% CI: [1.4 months; not estimable)).

6.6.4 INTRACRANIAL DURATION OF RESPONSE ACC. RANO

The analysis is restricted to patients with CR or PR as intracranial BOR according to RANO.

Intent-to-treat Population

Seven patients were analysed including 5 patients having an event (4 PD, 1 deaths) and 2 patients being censored.

Estimates for duration of response		
Quartile	**Estimate**	**95% CI**
Lower	1.4 months	[1.3 months; 3.6 months)
Median	3.6 months	[1.3 months; not estimable)
Upper	not estimable	[1.4 months; not estimable)

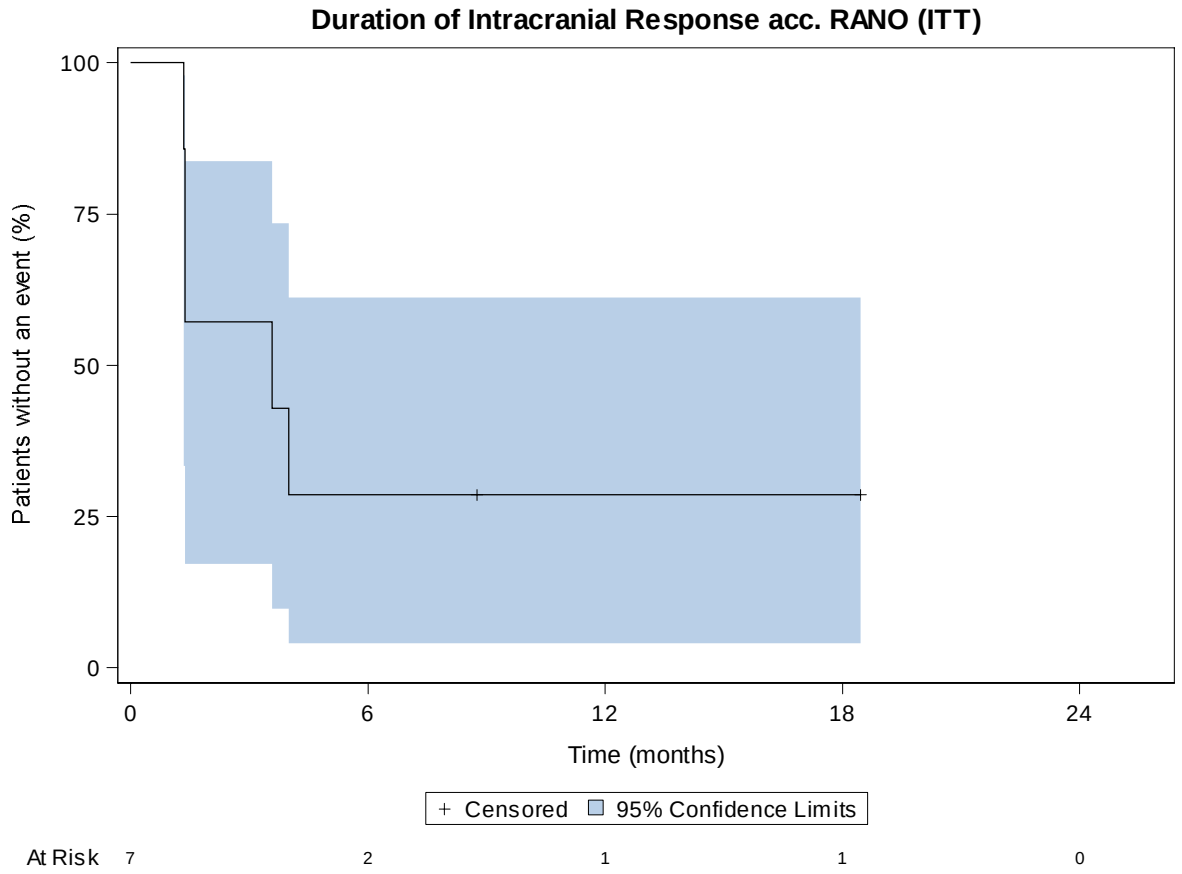

Figure 4: Kaplan Meier Plot Duration of Intracranial Response acc. RANO in ITT population

Per Protocol Set

6 patients analysed (4 events, 2 censored). Median duration of response 3.8 months (95% CI: [1.3 months; not estimable)).

6.6.5 EXTRACRANIAL DURATION OF RESPONSE ACC. RECIST 1.1

The analysis is restricted to patients with CR or PR as extracranial BOR according to RECIST 1.1.

Intent-to-treat Population

6 patients were analysed including 4 having an event (1 PD and 3 deaths) and 2 being censored.

Estimates for duration of response		
Quartile	**Estimate**	**95% CI**
Lower	8.2 months	[3.8 months; 18.1 months)
Median	17.9 months	[3.8 months; not estimable)
Upper	18.1 months	[3.8 months; not estimable)

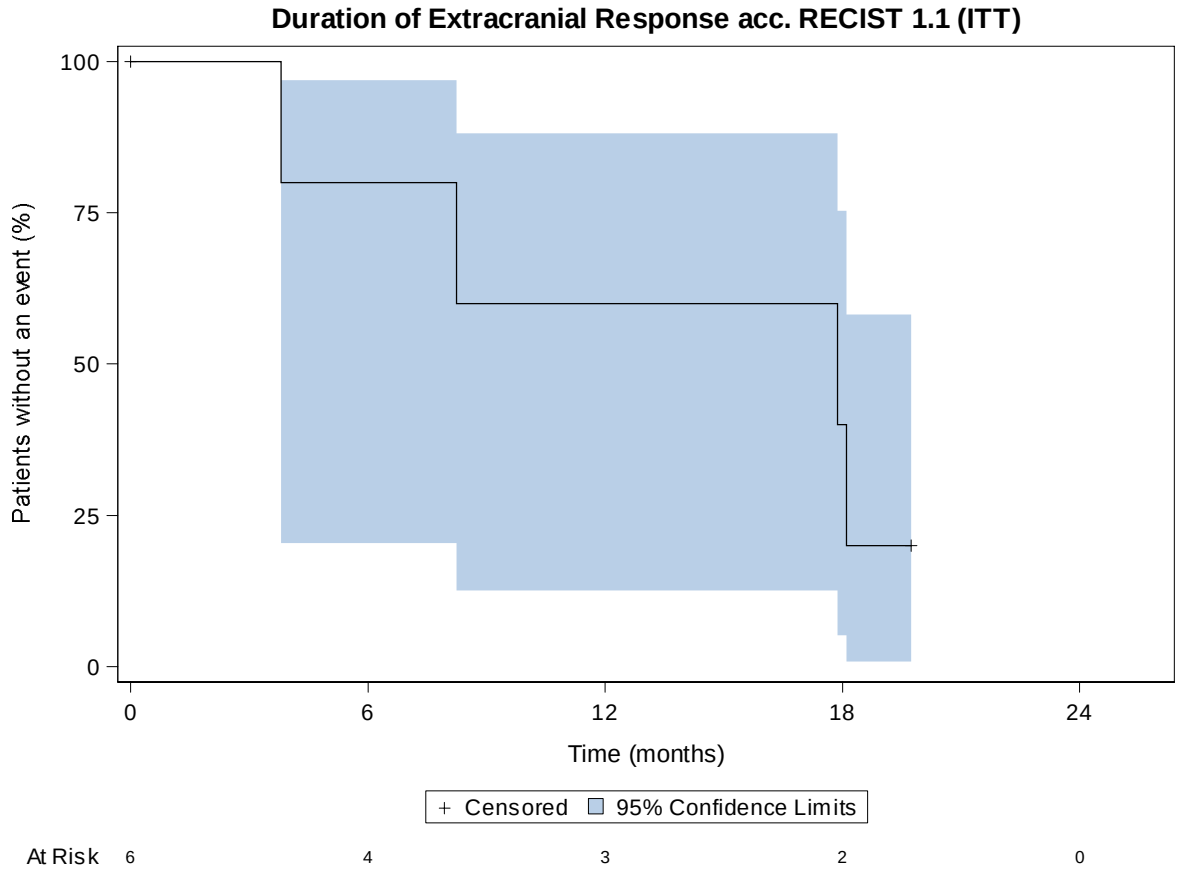

Figure 5: Kaplan Meier Plot Duration of Extracranial Response acc. RECIST 1.1 in ITT population

Per Protocol Set

5 patients analysed (3 events, 2 censored). Median duration of response 13.0 months (95% CI: [3.8 months; not estimable)).

6.6.6 PROGRESSION FREE SURVIVAL

Intent-to-treat Population

In the ITT analysis, 16 of 20 patients had an event (15 PD, one death) and 4 patients were censored. Median time to progression was 4.0 months (95% CI 2.8 months to 5.2 months).

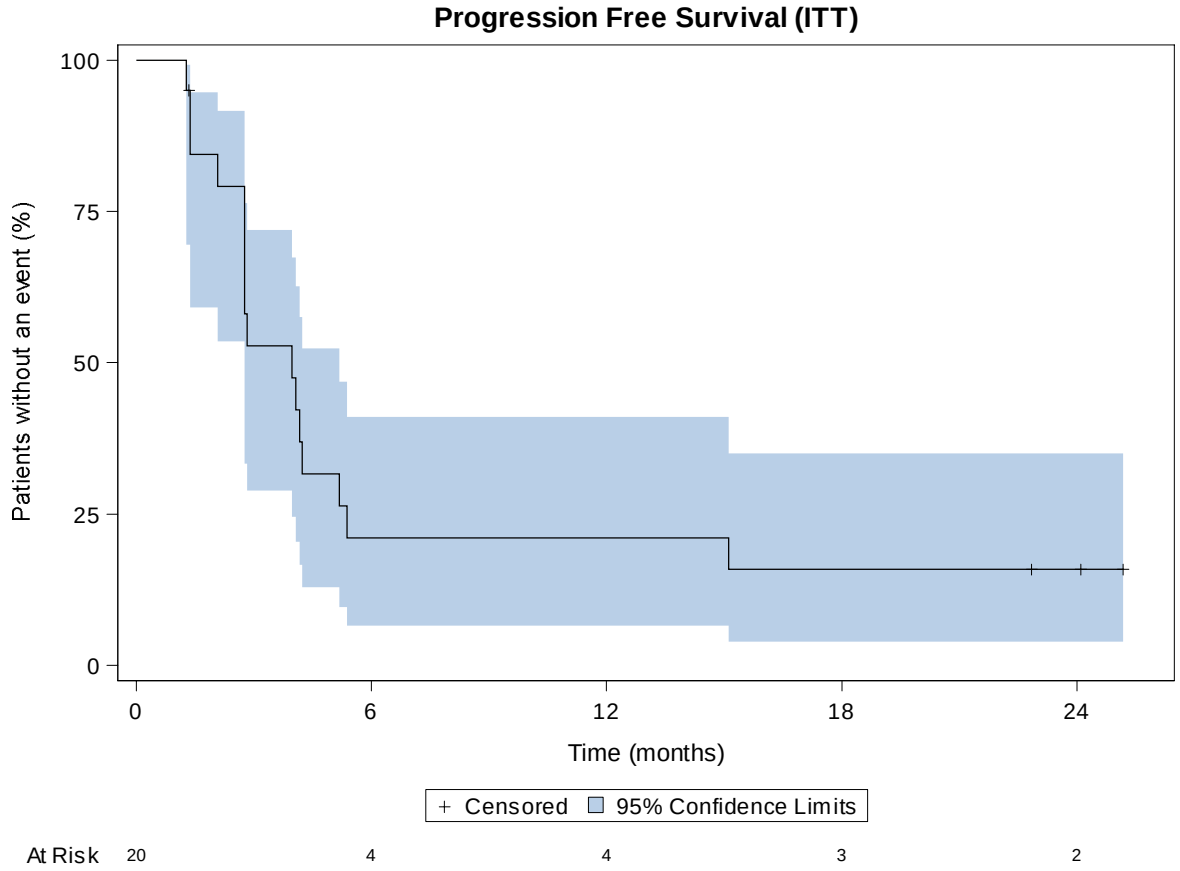

Figure 6: Kaplan Meier Plot Progression Free Survival in ITT population

Rate of Progression Free Survival		
Time Point	**Estimate**	**95% CI**
6 months	21.1%	[6.6%; 41.1%]
12 months	21.1%	[6.6%; 41.1%]
18 months	15.8%	[3.9%; 35.0%]
24 months	15.8%	[3.9%; 35.0%]

Per Protocol Set

14 of 18 patients had an event and 4 patients were censored. Median time to progression was 4.1 months (95% CI 2.8 months to 5.4 months). PFS rate after one year amounts to 23.6% (95% CI [7.3%; 45.0%]) and after two years 17.7% (95%CI [4.4%; 38.4%]).

6.6.7 INTRACRANIAL PROGRESSION FREE SURVIVAL

Intent-to-treat Population

In the ITT analysis, 16 of 20 patients had an event and 4 patients were censored. Median time to intracranial progression was 4.1 months (95% CI 2.8 months to 5.4 months).

Intracranial PFS rate after one year amounts to 21.1% (95% CI [6.6%; 41.1%]) and after two years 15.8% (95%CI [3.9%; 35.0%]).

Per Protocol Set

14 of 18 patients had an event and 4 patients were censored. Median time to intracranial progression was 4.2 months (95% CI 2.8 months to 7.5 months). PFS rate after one year amounts to 23.6% (95% CI [7.3%; 45.0%]) and after two years 17.7% (95%CI [4.4%; 38.4%]).

6.6.8 EXTRACRANIAL PROGRESSION FREE SURVIVAL

The analysis is restricted to patients with extracranial involvement with any re-staging by CT.

Intent-to-treat Population

In the ITT analysis, 12 of 16 patients had an event and 4 patients were censored. Median time to extracranial progression was 11.0 months (95% CI 5.5 months to 22.5 months).

One patient without any re-staging of extracranial involvements by CT was not included in this analysis.

Extracranial PFS rate after one year amounts to 49.2% (95% CI [23.6%; 70.6%]). Two year estimates are not available as the last patient under observation was censored after 22.9 months.

Per Protocol Set

11 of 14 patients had an event and 3 patients were censored. Median time to extracranial progression was 10.2 months (95% CI 4.2 months to 20.5 months). Extracranial PFS rate after one year amounts to 41.7% (95% CI [16.4%; 65.4%]).

6.6.9 OVERALL SURVIVAL

Intent-to-treat Population

In the ITT analysis, 11 of 20 patients had an event and 9 patients were censored. Median time to death was 20.9 months (95% CI [8.7 months; not estimable)). Only one early censoring caused by premature termination of the clinical study was observed.

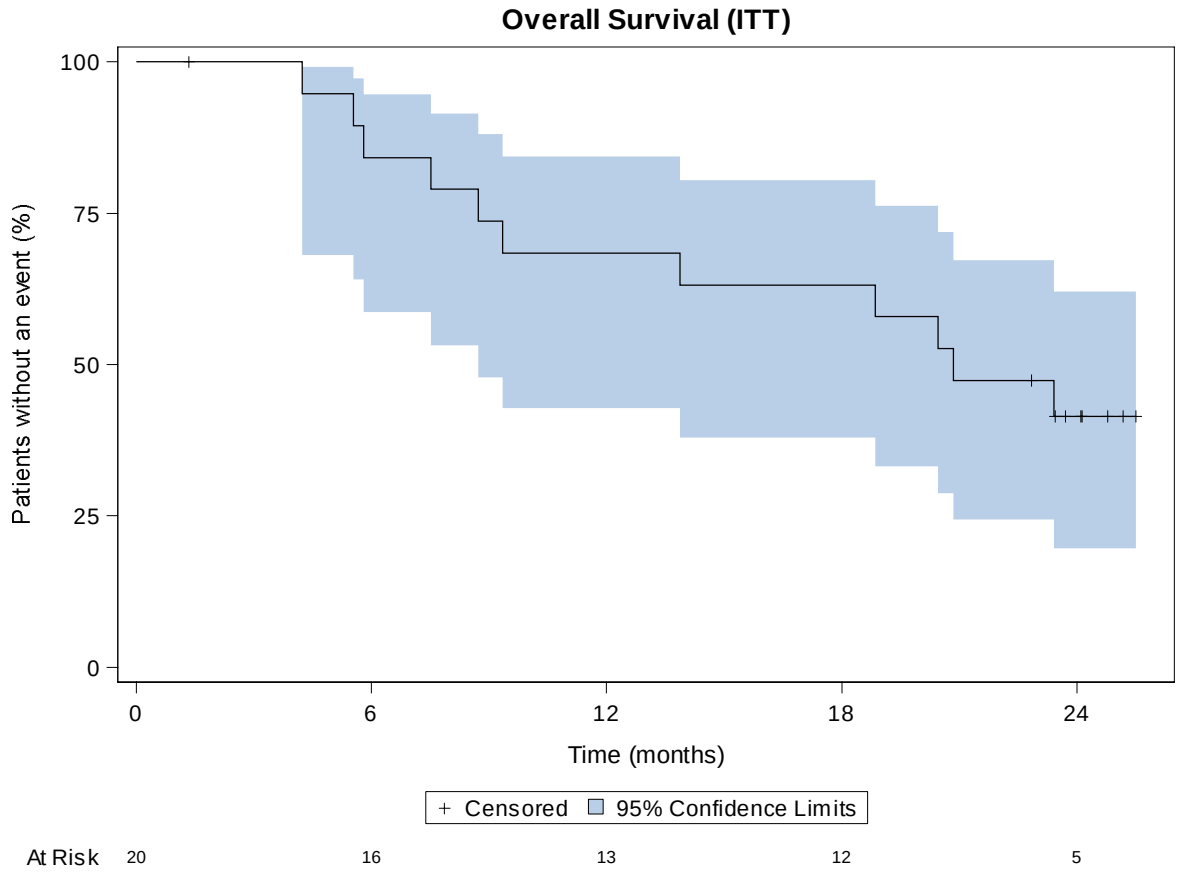

Figure 7: Kaplan Meier Plot Overall Survival in ITT population

Rate of Overall Survival		
Time Point	**Estimate**	**95% CI**
6 months	84.2%	[58.7%; 94.6%]
12 months	68.4%	[42.8%; 84.4%]
18 months	63.2%	[37.9%; 80.4%]
24 months	41.4%	[19.6%; 62.1%]

Per Protocol Set

10 of 18 patients had an event and 8 patients were censored. Median time to death was 20.5 months (95% CI [7.5 months; not estimable)). Overall survival rate after one year amounts to 64.7% (95% CI [37.7%; 82.3%]) and after two years 40.3% (95%CI [17.6%; 62.2%]).

6.7 SECONDARY ENDPOINTS OF SAFETY

6.7.1 ADVERSE EVENTS

All patients of the Intent-to-treat population had at least one adverse event. In total, 368 events were reported. The following tables contain data on their frequencies.

Event	No. of Events	Freqency of Patients	95% CI for Frequency of Patients with event
Adverse Event	368	20 / 20 (100%)	[83.2%; 100%]
AE grade>=3	50	16 / 20 (80.0%)	[56.3%; 94.3%]
AE grade=3	47	16 / 20 (80.0%)	[56.3%; 94.3%]
AE grade=4	3	3 / 20 (15.0%)	[3.2%; 37.9%]
AE grade=5	0	0 / 20 (0.0%)	[0.0%; 16.8%]
AE possibly related to IMP	229	20 / 20 (100%)	[83.2%; 100%]
AE possibly related to Vemurafenib	220	20 / 20 (100%)	[83.2%; 100%]
AE possibly related to Cobimetinib	170	20 / 20 (100%)	[83.2%; 100%]
AE grade>=3 possibly related to IMP	33	12 / 20 (60.0%)	[36.1%; 80.9%]
AE grade=3 possibly related to IMP	30	12 / 20 (60.0%)	[36.1%; 80.9%]
AE grade=4 possibly related to IMP	3	3 / 20 (15.0%)	[3.2%; 37.9%]
AE grade=5 possibly related to IMP	0	0 / 20 (0.0%)	[0.0%; 16.8%]
AE possibly related to prior SRS	14	10 / 20 (50.0%)	[27.2%;72.8%]
AE grade>=3 possibly related to prior SRS	1	1 / 20 (5.0%)	[0.1%; 24.9%]
AE grade=3 possibly related to prior SRS	1	1 / 20 (5.0%)	[0.1%; 24.9%]
AE grade=4 possibly related to prior SRS	0	0 / 20 (0.0%)	[0.0%; 16.8%]
AE grade=5 possibly related to prior SRS	0	0 / 20 (0.0%)	[0.0%; 16.8%]

6.7.2 ADVERSE EVENTS OF SPECIAL INTEREST

16 AESI in 12 patients were observed.

Event	No. of Events	Freqency of Patients	95% CI for Frequency of Patients with event
Adverse Event of Special Interest	16	12 / 20 (60.0%)	[36.1%; 80.9%]
AESI CNS haemorrhage	2	2 / 20 (10.0%)	[1.2%; 31.7%]
AESI CPK increased, CTCAE grade >= 3	4	4 / 20 (20.0%)	[5.7%; 43.7%]

Event	No. of Events	Freqency of Patients	95% CI for Frequency of Patients with event
AESI Diarrhea, CTCAE grade >= 3	1	1 / 20 (5.0%)	[0.1%; 24.9%]
AESI Haemorrhage event, CTCAE grade >= 3	0	0 / 20 (0.0%)	[0.0%; 16.8%]
AESI Heart failure	0	0 / 20 (0.0%)	[0.0%; 16.8%]
AESI LVEF reduction, CTCAE grade >= 2	0	0 / 20 (0.0%)	[0.0%; 16.8%]
AESI Photosensitivity, CTCAE grade >= 3	0	0 / 20 (0.0%)	[0.0%; 16.8%]
AESI Potentiation of radiation toxicity	0	0 / 20 (0.0%)	[0.0%; 16.8%]
AESI QT interval prolongation, CTCAE grade >= 3	0	0 / 20 (0.0%)	[0.0%; 16.8%]
AESI Radionecrosis	1	1 / 20 (5.0%)	[0.1%; 24.9%]
AESI Rash, CTCAE grade >= 3	4	4 / 20 (20.0%)	[5.7%; 43.7%]
AESI Retinal vein occlusion	0	0 / 20 (0.0%)	[0.0%; 16.8%]
AESI Rhabdomyolysis	0	0 / 20 (0.0%)	[0.0%; 16.8%]
AESI Serous retinopathy	4	3 / 20 (15.0%)	[3.2%; 37.9%]
Treatment-emergent ALT or AST > 3 x baseline value in combination with • total bilirubin > 2 x ULN (of which > 35% is direct bilirubin) or • clinical jaundice	0	0 / 20 (0.0%)	[0.0%; 16.8%]

6.7.3 ADVERSE EVENTS LEADING TO TREATMENT DISCONTINUATION

In 3 patients, both IMP were withdrawn due to the following adverse events:

- serous retinopathy (male patient)
- SAE pneumonitis (female patient)
- diarrhea, general physical health deterioration, SAE CPK increased, SAE renal failure (male patient)

Event	No. of Events	Freqency of Patients	95% CI for Frequency of Patients with event
AE leading to interruption of IMP	45	16 / 20 (80.0%)	[56.3%; 94.3%]
AE leading to interruption of Vemurafenib	41	16 / 20 (80.0%)	[56.3%; 94.3%]
AE leading to interruption of Cobimetinib	32	12 / 20 (60.0%)	[36.1%; 80.9%]

Event	No. of Events	Freqency of Patients	95% CI for Frequency of Patients with event
AE leading to withdrawal of IMP	6	3 / 20 (15.0%)	[3.2%; 37.9%]
AE leading to withdrawal of both IMP	6	3 / 20 (15.0%)	[3.2%; 37.9%]
AE leading to withdrawal of Vemurafenib	6	3 / 20 (15.0%)	[3.2%; 37.9%]
AE leading to withdrawal of Cobimetinib	6	3 / 20 (15.0%)	[3.2%; 37.9%]

6.7.4 SERIOUS ADVERSE EVENTS

In total, 25 serious adverse events were reported in 15 patients. None of these events were life-threatening (grade 4) or fatal (grade 5).During the whole study period, two SUSAR were reported to competent authorities (one malaise and one renal failure).

Event	No. of Events	Freqency of Patients	95% CI for Frequency of Patients with event
Serious Adverse Event	25	15 / 20 (75.0%)	[50.9%; 91.3%]
SAE grade>=3	22	13 / 20 (65.0%)	[40.8%; 84.6%]
SAE grade=3	22	13 / 20 (65.0%)	[40.8%; 84.6%]
SAE grade=4	0	0 / 20 (0.0%)	[0.0%; 16.8%]
SAE grade=5	0	0 / 20 (0.0%)	[0.0%; 16.8%]
SAE related to IMP acc. investigator	11	8 / 20 (40.0%)	[19.1%; 63.9%]
SAE possibly related to Vemurafenib	11	8 / 20 (40.0%)	[19.1%; 63.9%]
SAE possibly related to Cobimetinib	8	6 / 20 (30.0%)	[11.9%; 54.3%]
SAE grade>=3 related to IMP	10	7 / 20 (35.0%)	[15.4%; 59.2%]
SAE grade=3 related to IMP	10	7 / 20 (35.0%)	[15.4%; 59.2%]
SAE grade=4 related to IMP	0	0 / 20 (0.0%)	[0.0%; 16.8%]
SAE grade=5 related to IMP	0	0 / 20 (0.0%)	[0.0%; 16.8%]
SAE related to prior SRS	2	2 / 20 (10.0%)	[1.2%; 31.7%]
SAE grade>=3 related to prior SRS	1	1 / 20 (5.0%)	[0.1%; 24.9%]

The most frequent SAE related to Vemurafenib and/or Cobimetinib were maculopapular rash, renal disorders and malaise.

6.8 QUALITY OF LIFE

6.8.1 FUNCTIONAL ASSESSMENT OF CANCER THERAPY-BRAIN QUESTIONNAIRE

The questionnaires was answered by patients directly before starting a new therapy cycle. The score ranges from 0 to 200 points with higher values indicating better quality of life. At baseline, the median total score of FACT-Br amounts to 156 points (interquartile range 138 to 168 points) in our study population.

In a linear mixed model with patient as random effect, no impact of time course, i.e. therapy cycle, was observed (p=0.9991). From the 13th cycle onwards, the QoL questionnaire was answered by less than 6 patients. Therefore, the mixed model was restricted to cycle 1 until cycle 12.

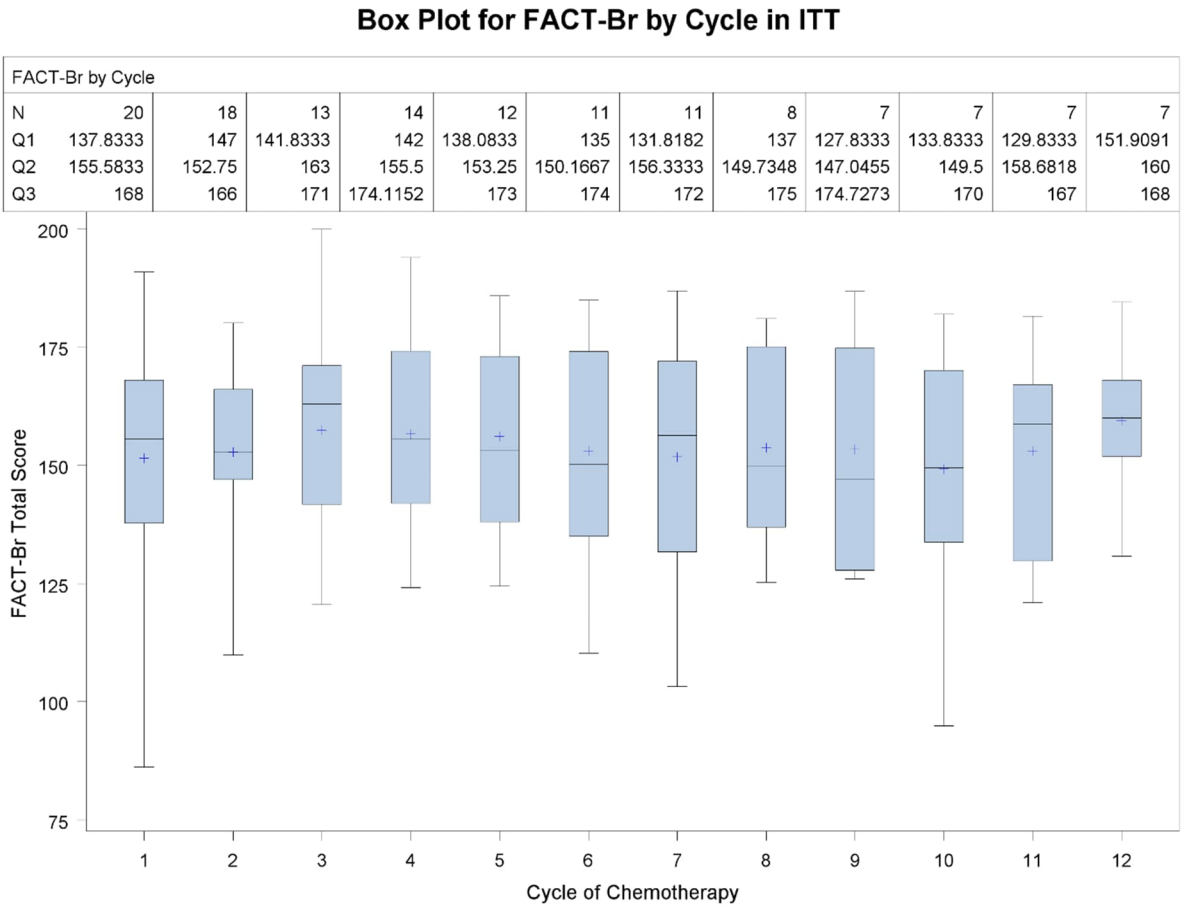

Figure 8: Box Plot for total score of FACT-Br
(N = number; Q1 = lower quartile; Q2 = median; Q3 = upper quartile)

6.9 COVARIATES

None of the investigated impact factors showed a statistically significant influence on primary and secondary endpoints. It needs to be stressed, that the case numbers are very low and the trial was not powered for this investigation at all. Thus, it is almost impossible to show statistical correlations.

7 CONCLUSION

Combining stereotactic radiosurgery (SRS) and active systemic therapy achieved favourable survival outcomes in patients with melanoma brain metastases in retrospective analyses (Rauschenberg et al. (2019); Dohm et al. (2023)).

This open-label multicenter phase II clinical trial evaluated the safety and efficacy of vemurafenib (Zelboraf®) plus cobimetinib (Cotellic®) after radiosurgery in patients with active BRAF-V600-mutant melanoma brain metastases.

The primary objective was to assess the intracranial best overall response rate (BORR) using modified RECIST v1.1 criteria.

Secondary endpoints included extracranial and whole body BORR, intra- and extracranial duration of response, progression-free and overall survival, safety as well as quality of life.

A total of 20 (10 male, 10 female) patients ≥ 18 (median 57) years of age with histologically confirmed AJCC stage IV metastatic BRAF-V600-mutant melanoma were analysed. They received SRS of at least one measurable, previously irradiated intracranial target lesion (≥ 0.5 to ≤ 4 cm in diameter) up to 21 days before starting targeted therapy.

Patients had an ECOG performance status of 0-1 and 65 % received prior systemic therapies. Most of them (85 %) also had extracranial disease. Patients with leptomeningeal or more than 10 measurable brain metastases and patients who were not stable on corticosteroids were excluded.

The primary endpoint of this study was met with an intracranial BORR of 65 % (95% CI [40.8%; 84.6%]). However, the median duration of response and progression-free survival were short (both 4 months versus 13 and 11 months extracranial, respectively). Fiveteen patients developed progressive disease, most of them new intracranial lesions. Median overall survival was 21 months.

The toxicity profile of Vemurafenib and Cobimetinib was similar to that reported in previous studies. New safety signals were not observed. 40 % of the patients experienced at least one serious adverse event related to the study treatment (mainly rash and renal disorders). Toxicity could be managed by dose interruptions or reductions. Only three patients discontinued treatment due to adverse events.

Two cases of intracranial haemorrhage were observed and assessed as not severe. One patient developed a radionecrosis, an expected adverse event of radiosurgery.

All in all, the safety profile of the combination appears to be acceptable and manageable.

Although the non-randomised one-arm design as well as the small and inhomogeneous sample size were limitations of the study, these data support a mutidisciplinary approach to melanoma brain metastases, with BRAF-/MEK inhibitors that play a relevant role in the therapeutic landscape, considering their rapid efficacy and high response rates in both asymptomatic and symptomatic brain metastases, in particular in the second-line setting.

8 PUBLICATIONS

Clinicaltrials.gov: https://www.clinicaltrials.gov/study/NCT03430947

9 SIGNATURES

The signing persons approve the report presented here by their signature. The described clinical trial was conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP) as well as the applicable legal regulations.

Sponsor

Prof. Dr. med. Friedegund Meier	Dresden, 24.04.24	Friedegund Meier
Name in block letters	Place, Date	Signature

Biostatistics

Evelyn Trips	Dresden, 13.05.24	Evelyn Trips
Name in block letters	Place, Date	Signature

10 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AR	adverse reaction
AST	aspartate aminotransferase
BID	twice a day
BOR	best overall response
BORR	best overall response rate
CI	confidence interval
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete remission
CSR	central serous retinopathy
CT	computed axial tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	data safety and monitoring board
ECOG	Eastern Cooperative Oncology Group
EoT	end of treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FACT-Br	Functional Assessment of Cancer Therapy-Brain questionnaire
GCP	Good Clinical Practice
HBV	hepatitis b virus
HCV	hepatitis c virus
ICH	International Conference on Harmonization
IMP	investigational medicinal product
INR	international normalized ratio
IQR	interquartile range
ITT	intention to treat
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
NE	not evaluable
NYHA	New York Heart Association
OD	once a day
OS	overall survival
PD	progressive disease

PFS	progression free survival
PPS	per protocol set
PR	partial response
QoL	quality of life
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumours
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SD	stable disease
SOP	standard operating procedure
SRS	stereotactic radiosurgery
SUSAR	suspected unexpected serious adverse reaction
TUD	Dresden University of Technology (Technische Universität Dresden)
ULN	upper limit of normal

11 REFERENCES

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