MEK inhibitor-associated retinopathy (MEKAR) in metastatic melanoma: Long-term ophthalmic effects

Urner-Bloch, U; Urner, M; Jaberg-Bentele, N; Frauchiger, A L; Dummer, R; Goldinger, S.M

Abstract: BACKGROUND: Mitogen-activated protein kinase kinase (MEK) inhibitors have aroused considerable interest in oncology. Activity has been demonstrated in various types of cancer, especially melanoma. MEK inhibitors induce a transient retinopathy, considered to be a class effect. At present, only sparse data are available on retinal effects with long-term MEK inhibition. PATIENTS AND METHODS: In this prospective, observational study, patients with advanced melanoma participating in different phase 1/2 or phase 3 clinical trials were treated with the MEK inhibitor binimetinib, with a v-Raf murine sarcoma viral oncogene homolog B (BRAF) inhibitor, or with combination therapy. They underwent regular ophthalmological examinations including determination of visual function, biomicroscopy, dilated fundoscopy and optical coherence tomography (OCT) for a period of up to 2 years. Retinopathy was diagnosed on defined OCT criteria. RESULTS: Sixty-two patients were investigated between 1st October 2011 and 31st July 2015: 13 were treated with the MEK inhibitor binimetinib alone, 10 with a selective BRAF inhibitor, and 39 with combination therapy. In 92% of patients on monotherapy and 100% of those on combination treatment, binimetinib caused dose-related lesions with serous neuroretinal detachments and oedema, strongly dependent on the time after medication. With continued treatment, retinal volume and thickness decreased to levels below baseline, without any apparent functional deficits or changes in structural integrity. CONCLUSIONS: Binimetinib induces a specific retinopathy with daily fluctuations depending on the time interval after medication. The retinopathy partially recovers, but can still be detected many months later. Retinal thinning, possible first signs of retinal atrophy have been observed after long-term treatment, but, so far, without functional relevance.

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Original Article

MEK inhibitor-associated retinopathy (MEKAR) in metastatic melanoma: long-term ophthalmic effects

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Abstract

Background: MEK inhibitors have gained large interest in oncology. Sensitivity to different cancer types, in particular melanoma, has been demonstrated. MEK inhibitors induce a transient retinopathy, which is considered a class effect. At present, only sparse data is available on retinal effects to long-term treatment with MEK inhibition.

Patients and methods: Patients with advanced melanoma treated either with MEK inhibitor binimetinib alone or in combination with a BRAF inhibitor participated in different phase 1/2 or phase 3 clinical trials underwent regular ophthalmological examinations including determination of visual function, biomicroscopy, dilated fundoscopy and optical coherence tomography (OCT). In this prospective, observational, study we collected ophthalmologic findings of these patients for a period of up to two years. The diagnosis of retinopathy was based on the presence of defined criteria in OCT.

Results: Between Oct 1, 2011, and July 31, 2015, 62 patients were treated with MEK inhibitor binimetinib alone or in combination with a BRAF inhibitor. In 92% to 100% of the patients, binimetinib alone or in combination caused dose-dependent retinal lesions with serous neuroretinal detachments and oedema, especially during the first weeks of treatment. There was a strong dependency from the time interval after medication. With ongoing treatment, retinal volume and thickness decreased to levels below baseline. No functional deficits or structural changes on high resolution OCT scans even after a treatment period up to two years were found.

Conclusions: Binimetinib induces a specific retinopathy with daily fluctuations depending on the time interval from medication intake. The retinopathy recovers over time, but may still be detectable after many months with subtle signs. Our measurements suggest a loss of retinal volume and thickness. No functional relevance was detected so far.

Key Message

MEK inhibitor binimetinib induces a dose- and time-dependent retinopathy with mild visual symptoms and reversible functional deficits. Daily fluctuations of the lesions are strongly associated with the time interval from medication intake and make the time point of examination crucial. Altogether, binimetinib is safe with regard to ocular adverse effects for treatment durations of up to two years.

Key words: MEK inhibition, retinopathy, melanoma, long-term treatment, optical coherence tomography, BRAF inhibition

Introduction

MEK inhibitors have gained large interest in oncology. They target a protein kinase involved in the Mitogen-Activated Protein Kinase (MAPK) pathway, which plays a relevant role in the development of various cancers [1]. Sensitivity to MEK inhibitors has been demonstrated as monotherapy or in combination in different cancer types. Moreover, tumour control in patients has been shown in clinical studies [2-7]. The introduction of novel treatment strategies such as targeted therapy and immunomodulation have prolonged patient survival in metastatic melanoma [8-11]. The addition of selective MEK inhibitors to the BRAF inhibitor treatment improved clinical outcome and delayed the development of drug resistance in BRAF mutated melanoma patients [12, 13]. Moreover, MEK inhibitors have demonstrated activity in NRAS mutated melanoma as well [2]. Common MEK inhibitor-related adverse events include acneiform skin rash, oedema, retinopathy and diarrhoea [14, 15]. Using combined therapy regimens many adverse events observed in BRAF monotherapy disappear or decrease in frequency. However, drug-related adverse events typical for MEK inhibitors, including retinal events, persist [8-10]. Some clinical features of MEK inhibitor-associated retinopathy, resembling to the well-known central serous chorioretinopathy [16], have been described in two studies with about 30 patients and in three small case series [15, 17-20]. At present, no long-term data is available. In this work, we investigated the ophthalmological effects of the selective MEK inhibitor binimetinib alone or in combination with other kinases including the BRAF inhibitor encorafenib over many months.

Patients and methods

Study design and participants

For this prospective, observational study, patients with advanced BRAF- and NRAS-mutant cutaneous melanoma were observed with focus on MEK inhibitor treatment-related ocular side effects during treatment with binimetinib alone or binimetinib in combination with RAF inhibitors for a period up to two years.

Patients were recruited from seven clinical trials: phase 1/2 open-label studies with binimetinib as monotherapy (NCT01320085), binimetinib in combination with the pan-inhibitor RAF265 (NCT01352273), binimetinib in combination with the selective BRAF inhibitor encorafenib (NCT01543698), binimetinib in combination with encorafenib and a third agent after progression (NCT02159066), or binimetinib added to treatment after relapse on encorafenib monotherapy (NCT01820364). Patients were also included from Phase 3 two- or three-arm randomized, prospective, open label studies: binimetinib monotherapy versus dacarbazine in patients with NRAS Q61 mutation positive melanoma (NCT01763164) or a combination of encorafenib plus binimetinib versus monotherapy with either encorafenib or vemurafenib (NCT01909453).

Patients were treated at the Department of Dermatology, University Hospital of Zurich. They underwent regular ophthalmological examinations according to the respective study protocols. Patients with an increased risk of retinal vein thrombosis, a history of vascular occlusion or previous central serous chorioretinopathy (CSR) were excluded. We assigned the patients according to their treatment in the context of the above mentioned trials to the following groups: binimetinib monotreatment, combined treatment with RAF inhibitors, and selective BRAF inhibitor monotreatment (**Table 1**). Patients with any pre-existing eye condition were analysed separately and reported in a separate paragraph.

All patients gave written informed consent and all aspects of the study were approved by the local Ethics Committee.

Procedures

All patients underwent full ophthalmological examinations at regular intervals, in accordance with each trial protocol as described elsewhere [15]. Briefly, examinations included an ophthalmological history, a record of the time and the dose of medication, determination of best corrected visual acuity, static perimetry (patients in phase 1/2 studies), slit-lamp examination, applanation tonometry, dilated fundoscopy, and multimodal imaging, especially optical coherence tomography (OCT). At each visit at least an OCT volume scan positioned on the fovea with the same acquisition protocol and rescan technology was performed. Segmentation errors were manually corrected. Only scans with good quality from patients with stable fixation were included. Blue laser autofluorescence has been recorded in all patients after a treatment duration of one year, in case of altered visual acuity, or in the presence of symptoms.

Outcomes

Incidence and severity of ocular side effects during long-term treatment with binimetinib were evaluated with the assessment of ocular symptoms, changes in visual function, slit lamp, and retinal findings. In fundoscopy we defined the presence of retinopathy if localized lesions were visible or if the typical bright retinal reflexes were blunted. An OCT positive retinopathy was defined in the presence of serous exudations and/ or oedema of the outer retinal layers. Evaluation of all possible retinal adverse events were assessed according to the same criteria for each session with regard to the morphology of the lesions (localized, bullous or widely extended, flat serous neuroretinal detachments), the location (foveal, extrafoveal or both), the presence of oedema, and the detection of segmentation errors. Oedema of the outer layers was defined as an increase in central retinal thickness (> 10µm) compared to baseline values (Heyex eye explorer software Version 1.9.10.0; Viewing module 6.3.4.0; Heidelberg Engineering, Heidelberg, Germany) and the appearance of four clearly separated, strongly reflective bands of the outer retina.

Statistical analysis

All statistical analyses were performed with R (R Development Core Team, 2015) using the "lme4"- and "lmerTest" packages [21, 22]. Linear mixed model analyses were used to assess influences on visual acuity, central retinal thickness and retinal volume. The dose of binimetinib, treatment with a RAF inhibitor, duration of treatment, and the time elapsed since medication were introduced as independent variables in the mixed model analysis. The subject variable was added as a random intercept to the model. Baseline values (before the start of treatment) were used as the reference category. If not otherwise indicated, figures show mean ± standard deviation. P-values < 0.05 were considered to be statistically significant.

Results

Between Oct 1, 2011, and July 31, 2015, 62 patients were enrolled and evaluated at regular intervals with median observation period of 170 days (IQR 115 – 280 days, including examinations after treatment stop). Of the 62 patients, 13 were treated with binimetinib monotherapy, 10 with selective BRAF inhibitor monotherapy, and 39 with combination therapy. Seventeen patients on binimetinib alone or in combination were examined after treatment stop. Details of the patient characteristics are given in **Table 1**.

MEK inhibitor-associated retinopathy was found in 12 of 13 patients during binimetinib monotherapy (92%), and in all 39 patients undergoing combination therapy. Selective BRAF inhibitor monotreatment caused no retinal changes. The sensitivity of biomicroscopy was 72.5% in detecting the typical lesions or evidence of oedema compared to OCT.

Five of thirteen patients (38%) on binimetinib monotherapy and 27 of 39 patients (69%) on combination therapy reported symptoms, while in patients undergoing RAF inhibitor monotherapy, two of ten patients (20%) were symptomatic (**Table 1**). Visual disturbances occurred especially during the first four weeks of treatment. On resuming binimetinib therapy after a treatment break, similar symptoms were experienced but were less pronounced. The

presence of visual symptoms was highly predictive for the detection of a retinopathy in OCT measurements (odds ratio 2.0; 95% CI 1.4 to 2.6; $p < 0.001$). This is, however, to be considered under the fact that only 34 of 51 (67%) of the patients having an OCT-positive retinopathy indicated visual symptoms.

With regard to visual function, a dose-dependent attenuation of visual acuity was found related to the time point of binimetinib intake ($p < 0.001$ and $p = 0.007$, **Supplementary table S1)**. Though, no influence was observed with regard to the duration of binimetinib treatment ($p=0.118$). Binimetinib therefore transiently attenuates visual acuity after medication intake, but even a prolonged exposure had no long-term effect on visual acuity. With regard to the results from perimetry, no significant changes in response to treatment with binimetinib were detected (mean defect versus values at baseline, $p=0.979$). No abnormalities in Roth 28-Hue Colour tests were observed after treatment periods of 6 to 24 month (d 3 colour confusions per eye).

In slit lamp examination, no evident pathologies were detected during treatment with binimetinib or a BRAF inhibitor, with the exception of two patients who had previously been treated with ipilimumab. In these two patients, bilateral signs of an earlier anterior uveitis with posterior synechiae were found at screening. A third patient had a relapsing uveitis anterior together with other manifestations of a sarcoidosis during the study treatment. The condition of these patients was well controlled with local treatment. Three patients had intermittently elevated intraocular pressure together with general oedema.

In fundoscopy, multiple, mainly bilateral, bullous lesions, often a larger one over the fovea, but distributed also far beyond the vascular arcades were found in patients on binimetinib alone and in combination with RAF265. The greyish-yellow round or oval lesions of various sizes were easy to overlook. They were not very prominent on biomicroscopy either. On combined treatment with binimetinib and encorafenib, larger localised bullous lesions have been found. However, only reduced retinal reflections and slightly blurred optic nerve

margins as an evidence of retinal oedema remained after many months of treatment. These affected patients were extremely photosensitive for many months and did not tolerate fundoscopy.

In contrast to fundoscopy, the examination with the scanning laser ophthalmoscope (SLO) was better accepted allowing questionable retinal lesions to be identified clearly. No abnormalities were found in blue laser autofluorescence. Enhanced depth imaging (EDI) of choroidal thickness during active retinopathy was within the normal age dependent limits.

The lesions (bullae, cleft or oedema) in OCT were most often observed both foveal and extrafoveal (**Figure 1A)**. The morphological appearance of the retinal lesions differed between binimetinib mono- and combined treatment (**Table 1**). Bullous lesions were more often visible on monotreatment. On combined treatment, the typical finding was a flat neuroretinal detachment which expanded over a large part of the posterior pole (**Figure 1B**). This flat neuroretinal detachment was not identifiable on fundoscopy and was seen in the OCT scan only. Especially patients with bullae or oedema in the OCT measurements reported on visual disturbances (odds ratios: 5.7 and 3.6, respectively; 95% confidence intervals: 3.1 to 10.7 and 2.0 to 6.3, respectively; both p-values < 0.001), while a flat neuroretinal detachment was unlikely to provoke symptoms ($p = 0.080$).

The findings in OCT depended on the time that had elapsed since drug administration. The maximal changes in the retina occurred within four hours after medication intake (**Figure 2**). Shortly before administration of the drug, the same patients showed in some cases oedema, but most often no evidence of pathology. 30 minutes after medication intake, subtle segmentation errors in the outer retinal layers (pigment epithelium, interdigitation zone), occasionally with incipient oedema, appeared as an early sign of the drug effect. In some cases, this irregularity affected only the retinal pigment epithelium (RPE) (**Supplementary Figure S1**). About 60 minutes after drug administration, a mainly central thickening of the outer retinal layers appeared; another 15 to 30 minutes later, the first signs of an exudate were

detectable (**Figure 3**). These morphological changes resolved in the reverse order some four to five hours later.

Especially during the first weeks of treatment with binimetinib a dose-dependent increase of retinal volume, as well as an increase in central retinal thickness were observed (p-values < 0.001, **Supplementary Table S2-4**). These changes resolved gradually over 3-6 months and reached values that were even lower than at baseline within a year (**Figure 4, Supplementary Figure S2**). No influence of selective BRAF inhibitors on retinal parameters was found (**Supplementary Table S2-4**). On binimetinib monotherapy, 9 of 13 patients had to switch on intermittent treatment due to not eye-related adverse events. After each re-initiation, they experienced a relapse of a mild exudative retinopathy. All these patients on combined treatment continued over more than 6-12 months to develop flat neuroretinal detachments of variable amount or just only oedema during a short time window in response to medication.

In a separate analysis, 17 of the 62 patients were examined after the end of treatment with regard to potential retinal residues of binimetinib-induced retinopathy. All were symptom-free and visual function tests were unchanged from baseline. We found no signs of degeneration such as changes in pigmentation in fundoscopy or in autofluorescence. As reported during active treatment with binimetinib, a reduction in retinal volume and thickness below pre-treatment values was measured (**Figure 4, Figure S2**). This thinning of the retina persisted for at least a week after the end of treatment. The follow-up of surviving patients suggested a potential recovery. No irregularities in retinal architecture on OCT high resolution scans with a special attention to ellipsoid zone and outer nuclear layer were detected.

Seven patients with pre-existing eye disease were analysed separately. Pre-existing conditions included: unilateral or bilateral macular oedema with epiretinal gliosis (n=3), extensive drusen within a dry age-related retinopathy and glaucomatous optic atrophy with well-controlled intraocular pressure (n=1), traumatic optic atrophy (n=1), only one functional eye and extreme myopia (n=1), severe panuveitis following ipilimumab (n=1). All patients had the typical

serous neuroretinal detachments, which were well documented with OCT and proceeded a similar course to those seen in the other study participants (**Figure 5**). Groups of drusen often encouraged serous detachments, which then required a little longer to resolve.

Discussion

In the present article we describe for the first time ophthalmic long-term effects of binimetinib treatment alone or in combination with RAF inhibitors in advanced melanoma. Binimetinib induces a dose-dependent retinopathy in almost 100% of the patients. The morphological aspects of this retinopathy including bilateral neuroretinal detachments with daily fluctuations and oedema of the outer retinal layers are highly specific for the treatment with MEK inhibitors. Especially patients undergoing monotreatment tend to develop bullous lesions which more frequently induce visual disturbances. The addition of the selective BRAF inhibitor encorafenib modulates the aspect of the retinopathy to flat and more extended detachments. None of the patients experienced persistent functional deficits even after a treatment duration of up to two years. The use of OCT for diagnosis and follow-up is mandatory; fundoscopy detected 70% of the lesions only. After initial thickness increase the retinal measurements gradually decreased and reached values even below screening after six months. After treatment stop there seems to be a partial recovery of retinal values. At present, the clinical significance of this retinal thinning is not clear and has to be addressed in future research.

MEK inhibitor-induced retinopathy occurs in response to treatment with various types of MEK inhibitors and is therefore considered to be a class effect [15, 17, 18]. The MEK1/2 inhibitors, which have already been evaluated in clinical trials, show considerable differences in their pharmacokinetics. The T_{max} of binimetinib is about 1.18 hours and plasma half-life 8 hours. The corresponding half-lifes for cobimetinib and trametinib are approximately 2 days (49 hours) and 4.5 days (108 hours), respectively [4]. These characteristics might highly

influence the incidence of adverse events, including retinopathy (the detection is dependent on the time point of examination).

The term MEKAR is proposed in analogy to CAR, cancer associated retinopathy or MAR, melanoma associated retinopathy, both rare eye conditions with severe functional deficits observed in metastatic disease [23, 24]. Auto-immunologic based cross reactions between tumour antigens and retinal tissues were described. In MEK inhibitor treated patients a dysfunction of the highly active metabolism and fluid regulation of the retinal pigment epithelium (RPE), which is essential to supply the receptors, has been suggested as underlying aetiology [25]. This is supported by recent findings on functional deficits in investigations with electrophysiological methods [17]. Our findings confirm that the pathology is initiated at the outer retinal layers. In our observations, the first subtle changes in response to drug exposure were segmentation errors and oedema at the location of the RPE, followed by the interdigitation zone, which is attributed to the interdigitations of the apical processes of the RPE with the cone outer segments [26]. The appearance of the lesions is less pronounced after a few weeks of treatment, but still a time-dependent retinal response is observed. Taken into account that we observed a retinopathy in almost 100% of the binimetinib-exposed patients, this is unlikely the course of an allergic phenomenon or autoimmune reaction, but highly suggests a toxic reaction in response to MEK inhibitor exposure.

We found evidence of a reduction in retinal measurements to below baseline values and the maintenance of these lower values even after discontinuing the MEK inhibitor. At present, the underlying cause of this finding remains unclear. Findings on the progression of heredo-degenerative retinal disease, in particular age-related macular degeneration, or toxic retinopathy have shown that the functional capacity of a stressed pigment epithelium – and hence the receptors – remains intact for a limited time and is followed by atrophy [27-29]. Similarly a stress reaction and disturbance of homoeostasis in the skin and finally chronic changes have been shown [14]. Our findings suggest partial resolution of the retinal thinning

after end of treatment. However, persistent degeneration in most retinal diseases is a slow developing process and our observation period of two years is most likely too short.

With regard to patients with pre-existing eye disease, the exclusion of patients with a history of retinal vein occlusion from treatment with MEK inhibitors is probably not justified, as the pathogenesis of the condition that we describe is clearly different and involves a different retinal compartment. Venous occlusion and macular oedema occur in the inner retinal layers due to the dysfunction of the retinal vessels forming the inner blood-retinal barrier, while the pigment epithelium maintains the blood-retinal barrier to the choroid [30]. Classic central serous chorioretinopathy is thought to be primarily due to pathological changes in the choroid circulation, associated with a marked measurable thickening, and to hormonal influences [16].

Altogether, we demonstrate that a treatment with binimetinib is safe with regard to ocular adverse effects for a treatment duration of up to two years. Due to the fact that appearance of the retinal lesions is highly dose- and time-dependent, the time point of examination has strong diagnostic implications. In fundoscopy, about one third of the retinopathies are not detected, optical coherence tomography is therefore mandatory for a thorough monitoring of patients treated with all types of MEK inhibitors.

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Disclosures

U.U. and R.D. acted as consultants for Novartis.

Authors' contributions

U.U., R.D., S.M.G designed the study. U.U., N.B.J., and A.L.F. treated the patients and collected the data. M.U. made the statistical analysis and figures. U.U., M.U., R.D., S.M.G wrote the paper.

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Figure legends

Figure 1: Different aspects of binimetinib induced retinopathy in dependence of treatment. (A) left: binimetinib monotreatment 30mg BID: scanning laser ophthalmoscopy (SLO multicolour wide angle image) of the right eye demonstrates multiple bullous lesions distributed on the posterior pole; right: typical neuroretinal detachments on a horizontal line scan with optical coherence tomography (OCT) through the fovea (arrow). (B) Combined treatment with binimetinib 45mg BID and encorafenib 450mg QID, six months after treatment start: left: SLO image doesn't reveal any particular pathology, right: on OCT a flat and wide spread neuroretinal detachment and oedema of the outer retinal layers were discovered (arrow).

Figure 2. Course of retinal changes in patients during a time period of up to two years of treatment with binimetinib and RAF inhibitor (combination therapy) with regard to retinal volume (**A**), maximal (**B**) and minimal retinal thickness (**C**). The time difference to medication was d240min. Trend lines were smoothed using the 'stat_smooth' function of the ggplot2 package (method = 'loess') in R. Shading indicates 95% confidence intervals around the trend lines.

Figure 3. Development of an exudative retinal lesion: At the screening examination (A) scanning laser ophthalmoscopy (SLO) (left) and a high resolution horizontal line optical coherence tomography (OCT) scan through the fovea (right) demonstrates normal morphology, with three strongly reflective bands of the outer retina. (B) day 14 after treatment start with binimetinib BID 45mg and encorafenib QD 450mg, 9.5 hours after last medication: On the left in the SLO and on the right on the OCT scan a foveolar lesion was detectable with an enormous oedema of the outer retinal layers, mainly of the interdigitation zone (yellow arrow, measurement: 52µm). On the same day 90 minutes after the morning dose of the tablets (C) a bilateral subfoval neuroretinal detachment with serous exudation had

developped, also visible on ophthalmoscopy. (D) Two weeks later 110 minutes after medication, SLO (left) was almost unremarkable, on the OCT scan (right) now four strongly reflective bands were present, still as a sign of oedema of the outer retina. On later visits these daily fluctuations were still present, mostly not more as some 15µm.

Figure 4: Treatment-duration dependent changes of retinal volume (**A**), of maximal (**B**) and of minimal retinal thickness (**C**) in patients after intake of binimetinib (monotherapy or combined treatment). Retinal volume was measured in a 6mm circle diameter. Trend lines were smoothed using the 'stat_smooth' function of the ggplot2 package (method = 'loess') in R.

Figure 5: Resolvement of binimetinib-induced retinopathy in a patient with pre-existing retinal diseases. (A) Drusen maculopathy: left: SLO multicolour image: multiple bullous lesions, the perifoveal smaller yellow spots respresent drusen; right: a horizontal line scan demonstrates oedema of the outer retinal layers and subfoveal exudation, the multiple irregular elevations below the retinal pigment epithelium represent the drusen. (B) Drusen maculopathy: Eight days after end of treatment: retinal contours returned to baseline, the drusen were unchanged (arrow). (C) Severe epiretinal gliosis: left: SLO image showed many lesions of different size and irregular reflections from the retinal surface; right: on a horizontal line scan an enormous elevation of the central retina with oedema of all layers and neuroretinal detachments at several positions (arrows) were detected. (D) Severe epiretinal gliosis: after a treatment stop: the lesions almost disappeared.

Tables

Table 1. Baseline characteristics and incidence of retinopathy

	All patients (n=62)	Binimetinib monotherapy (n=13)	BRAF inhibitor monotherapy (n=10)	Combination therapy (n=39)
Male sex	39 (63%)	9 (69%)	6 (60%)	24 (62%)
Age (years)	55 (46-64)	61 (55-67)	57 (51-64)	53 (45-63)
Length of observation (days)	170 (115-280)	229 (78-314)	236 (168-324)	162 (116-263)
NRAS mutated melanoma	13 (21%)	12 (92%)	-	1 (3%)
End of treatment	37 (60%)	9 (69%)	10 (100%)	18 (46%)
RAF Inhibitor				
LGX818 (encorafenib)	43 (69%)	0	8 (80%)	35 (90%)
RAF265	4 (6%)	0	0	4 (10%)
Zelboraf (vemurafenib)	2 (3%)	0	2 (20%)	0
Number of OCT images	1233	277 (23%)	90 (7%)	866 (70%)
Symptoms present	34 (55%)	5 (38%)	2 (20%)	27 (69%)
Positive fundoscopy	37 (60%)	10 (77%)	0	27 (69%)
Positive OCT	51 (82%)	12 (92%)	0	39 (100%)
OCT morphology				
Bullae	29 (47%)	9 (69%)	0	20 (51%)
Cleft	33 (53%)	2 (15%)	0	31 (79%)
Oedema	51 (82%)	12 (92%)	0	39 (100%)

Data are n (%) or median (IQR). OCT=Optical coherence tomography.

Table 2. Mixed model analysis on changes of retinal volume in response to binimetinib therapy.

	Estimate (CI-95%)	**Significance**
Binimetinib dose, mg	0.0075 (0.0043, 0.0108)	p<0.001
RAF inhibitor	-0.0043 (-0.2310, 0.2224)	p=0.976
Treatment duration, d	-0.0003 (-0.0005, -0.0002)	p=0.001
Time elapsed since medication, min	-0.0004 (-0.0004, -0.0003)	p<0.001

The table shows estimates and corresponding 95% confidence intervals. Patients before begin of treatment with binimetinib, without RAF inhibitor therapy and before intake of medication have been defined as the reference group in the mixed model. RAF inhibitor treatment was defined as treatment with either encorafenib, RAF265, or vemurafenib. We controlled for subject using a random intercept. Dependent variable: retinal volume (mm^3).

Table 3. Mixed model analysis on changes of maximal retinal thickness in response to binimetinib therapy.

	Estimate (CI-95%)	**Significance**
Binimetinib dose, mg	0.75 (0.55, 0.93)	p<0.001
RAF inhibitor	-11.47 (-22.34, -0.60)	p=0.091
Treatment duration, d	-0.03 (-0.04, -0.02)	p<0.001
Time elapsed since medication, min	-0.01 (-0.02, -0.01)	p<0.001

The table shows estimates and corresponding 95% confidence intervals. Patients before begin of treatment with binimetinib, without RAF inhibitor therapy and before intake of medication have been defined as the reference group in the mixed model. RAF inhibitor treatment was defined as treatment with either encorafenib, RAF265, or vemurafenib. We controlled for subject using a random intercept. Dependent variable: maximal retinal thickness (µm).

Table 4. Mixed model analysis on changes of minimal retinal thickness in response to binimetinib therapy.

	Estimate (CI-95%)	**Significance**
Binimetinib dose, mg	0.68 (0.45, 0.91)	p<0.001
RAF inhibitor	-4.23 (-18.80, 10.38)	p=0.638
Treatment duration, d	-0.03 (-0.05, -0.02)	p<0.001
Time elapsed since medication, min	-0.01 (-0.02, -0.01)	p<0.001

The table shows estimates and corresponding 95% confidence intervals. Patients before begin of treatment with binimetinib, without RAF inhibitor therapy and before intake of medication have been defined as the reference group in the mixed model. RAF inhibitor treatment was defined as treatment with either encorafenib, RAF265, or vemurafenib. We controlled for subject using a random intercept. Dependent variable: minimal retinal thickness (µm).