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REVIEW ARTICLE

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Encorafenib in combination with binimetinib — a new therapeutic option with a favourable safety profile in the treatment of patients with advanced *BRAF* mutation-positive melanoma

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ABSTRACT

Encorafenib and binimetinib were registered in 2018 for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF V600* mutation. The results of the phase III study (Columbus) are very promising. Median PFS for patients who have received this treatment was 14.9 months, and the median OS was 33.6 months. The reduction of toxicity is the reason for the unique pharmacokinetic profile of this therapy. Knowledge about the adverse evets is important in the context of optimizing and individualizing treatment.

Key words: encorafenib, binimetinib, *BRAF*, melanoma, adverse events, safety of treatment

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In about 50% patients with a melanoma diagnosis in the dissemination stage, a *BRAF* gene mutation most commonly in exon 15 (over 95% cases) is detected. It causes the activation of mitogen-activated protein kinase (MAPK), which leads to the development and progression of melanoma [1]. The introduction of BRAF inhibitors (BRAFi) — vemurafenib in 2011 and dabrafenib in 2012 — caused a significant improvement in progression-free survival (PFS) and overall survival (OS) in comparison with the used then dacarbazine-based chemotherapy [2].

The advantages of using BRAFi in monotherapy are, however, limited mainly because of the emerging resistance due to MAPK pathway reactivation. Double inhibition of the MAPK pathway by using combined therapy based on BRAFi and MEKi (MEK inhibitors) allowed an improvement in results of treatment with decreased toxicity [3]. Among standard methods of treating patients with advanced melanoma are three combinations of BRAFi/MEKi (vemurafenib/cobimetinib, dabrafenib/trametinib, and encorafenib/binimetinib) [4]. The two first combinations have a comparable effectiveness in the context of treatment, with a median PFS of about 12 months and median OS of about 24 months. The above-mentioned drugs differ in their safety profiles and the occurring adverse events. For instance, fever was observed in 51–53% of patients treated with dabrafenib/trametinib, and this was the main reason for treatment interruption (in 30–32%) or dose reduction (13–14%). In turn, the strongest photosensitising effects were observed in the group of patients treated with vemurafenib/cobimetinib (in 48%) [2, 5].

On the basis of the results of a phase III trial (COLUMBUS), a third combination of drugs — encorafenib and binimetinib — was registered in the United States and in the European Union in 2018 for treating patients with advanced melanoma and *BRAF* mutation. Median PFS for patients receiving this treatment was 14.9 months, and median OS was 33.6 months [5]. Adverse events of any grade were reported less frequently in this group in comparison with patients treated with dabrafenib/trametinib or vemurafenib/cobimetinib [2, 5].

Encorafenib was found to have a long half-life (> 30 hours) in comparison with dabrafenib (2 hours) or vemurafenib (0.5 hours). Moreover, IC50 (one half of the maximal inhibitory concentration) is 40 nmol/l or less in most melanoma cell lines. For comparison, a higher concentration of dabrafenib (< 100 nmol/l) and a much higher concentration of vemurafenib (< 1 μmol/l) is required to inhibit proliferation in most cell lines, which may translate into a higher efficacy of encorafenib treatment with a simultaneous reduction in toxicity [4, 6].

One of the more serious adverse events after monotherapy with BRAF inhibitors is the induction of secondary neoplasms — most frequently cutaneous squamous-cell carcinoma (cuSCC). This is linked to paradoxical ERK activation or hyperactivation of ERK signalling by BRAF inhibitors in cells without the *BRAF* mutation (*BRAF* wild-type cells). The index of cuSCC induction is highly differentiated depending on the used BRAF inhibitor because ERK activation and the time of activation are unique for each inhibitor [6].

In 2016, in the biweekly Oncotarget, the results of studies performed at the MD Anderson University in Texas by Adelmann et al. were published, comparing the ranges of BRAF inhibitor concentrations (vemurafenib, dabrafenib, encorafenib LGX818 and PLX8394) required for paradoxical ERK activation. Encorafenib had the highest paradox index. This means that in comparison with other inhibitors it causes cuSC0,C to a much smaller extent, and a higher drug concentration is much better tolerated. Adverse events linked to paradoxical ERK activation are more common in the case of therapy with vemurafenib (18–19%) and dabrafenib (6–10%) in comparison with encorafenib (4%) [7].

So far, no clinical trial has been conducted directly comparing the action and safety profile of vemurafenib/cobimetinib, dabrafenib/trametinib, and encorafenib/binimetinib, and indirect comparison of the used combinations between clinical trials is of limited value.

Analysis of the results of phase III trials in which basic safety parameters were compared for dabrafenib/trametinib (COMBI-v), vemurafenib/cobimetinib (coBRIM), and encorafenib/binimetinib (COLUMBUS) is presented in Table 1. What is important, each trial comprised a comparative arm with 960 mg vemurafenib given two times per day [8]. Patients included in individual trials had similar characteristics; however, the proportion of persons with initial higher LDH activity above the upper range of the normal value in the coBRIM trial was higher than in the COMBI-v and COLUMBUS trials [8, 9].

The results of the first part of the phase III COLUMBUS trial indicate that encorafenib and binimetinib together show a favourable profile of effectiveness and tolerance, which is indicated by attainment of a higher median of dose intensity with a longer exposure to treatment. For the Columbus trial altogether 577 patients were randomised, and 570 who received treatment were included in the analysis of the safety profile. Patients were randomised in a 1:1:1 ratio (192 — encorafenib and binimetinib, 192 — encorafenib in monotherapy, 186 — vemurafenib in monotherapy). The median exposure time to the analysed treatment was greatest in the branch in which encorafenib was used in combination with binimetinib, and it was 51 weeks in comparison to using encorafenib in monotherapy (31 days) and vemurafenib in monotherapy (27 weeks) [10].

Knowledge of the safety profile, characteristic adverse events for selected combinations, and the potential time of their occurrence after initiation of therapy (Table 2) is important in the context of selection and optimisation of treatment in particular groups of patients [5]. The most important undesirable effects reported in the Columbus registration trial were evaluated by CTCAE (Common Terminology Criteria for Adverse Events) criteria and are presented in Figure 1.

Fever

In the COLUMBUS trial fever was reported much more frequently during vemurafenib treatment (in 30%). Encorafenib in monotherapy and in combination with binimetinib can also cause fever (in the COLUMBUS trial it was observed, respectively, in 16% and 18% patients), but it was reported much later after the moment of treatment initiation (median time to first occurrence 85 days [1–560] (Table 2) in comparison with vemurafenib — 19 days [2–619]). In general, in patients treated with encorafenib and binimetinib, this undesirable effect was grade 1, but was rarely the cause of dose reduction (4%) and interruption of treatment l (1 patient: < 1%) [5]. Fever for the encorafenib and binimetinib combination was in general limited to a single episode and was rarely recurrent (only in 5% patients), in contrast to the dabrafenib and trametinib combination, where it occurred much more frequently and was more often recurrent [8]. In the COMBI-V trial in the group of patients treated with dabrafenib and trametinib, fever was the most common reason for interrupting treatment

Table 1. Frequency of adverse events in combined therapy, which occurred in key clinical trials comparing BRAFi/MEKi combinations with vemurafenib [8]

Combination	Dabrafenib + trametinib		Vemurafenib + cobimetinib		**Encorafenib + binimetinib**	
Date at moment of analysis	13.03.2015		30.09.2015		19.05.2016	
Name of clinical trial	COMBI-V		coBRIM		COLUMBUS part 1	
All patients of treated population (analysis in agreement with planned treatment)	352 (350)		247 (247)		192 (192)	
Daily drug dose [mg]	300 + 2		1920 + 60		450 + 90	
Toxicity grade according to CTC AE	All	3–4	All	3–4	All	3–4
Skin complications [n (%)]						
Rash	84 (24.0)	3 (0.9)	101 (40.9)	13 (5.3)	27 (14.1)	2 (1.0)
Maculopapular rash	13 (3.7)	2 (0.6)	38 (15.4)	18 (7.3)	3 (1.6)	0
Dry skin	33 (9.4)	0	38 (15.4)	2 (0.8)	27 (14.1)	0
Pruritus	36 (10.3)	0	49 (19.8)	3 (1.2)	21 (10.9)	1 (0.5)
Erythema	35 (10.0)	0	26 (10.5)	0	13 (6.8)	0
Acne dermatitis	23 (3.6)	0	34 (13.8)	6 (2.4)	6 (3.1)	0
Baldness	23 (6.6)	0	41 (16.6)	1 (0.4)	26 (13.5)	0
Hyperkeratosis	18 (5.1)	0	25 (10.1)	1 (0.4)	27 (14.1)	1 (0.5)
Keratosis of hands and feet	–	–	5 (2.0)	0	17 (8.9)	0
Palmoplantar erythrodysesthesia	14 (4.0)	0	17 (6.9)	0	13 (6.8)	0
Solar keratosis	5 (1.4)	0	13 (5.3)	8 (3.2)	–	–
Keratosis pilaris	4 (1.1)	0	9 (3.6)	0	9 (4.7)	0
Hypersensitivity to light	15 (4.3)	0	84 (34.0)	1 (0.4)	8 (4.2)	1 (0.5)
Sunburn	3 (0.9)	0	37 (15.0)	2 (0.8)	0	0
Cutaneous squamous cell carcinoma	5 (1.4)	5 (1.4)	10 (4.0)	9 (3.6)	5 (2.6)	0
Keratoacanthoma	2 (0.6)	2 (0.6)	4 (1.6)	3 (1.2)	4 (2.1)	0
Skin papilloma	8 (2.3)	0	17 (6.9)	0	12 (6.3)	0
Basal cell carcinoma	3 (0.9)	2 (0.6)	15 (6.1)	14 (5.7)	3 (1.6)	0
Gastrointestinal complications [n (%)]						
Diarrhoea	120 (34.3)	4 (1.1)	150 (60.7)	16 (6.5)	70 (36.4)	5 (2.6)
Nausea	126 (36.0)	1 (0.3)	105 (42.5)	3 (1.2)	79 (41.1)	3 (1.6)
Vomiting	107 (30.6)	4 (1.1)	63 (25.5)	4 (1.6)	57 (29.7)	3 (1.6)
Stomachache	39 (11.1)	1 (0.3)	27 (10.9)	1 (0.4)	32 (16.7)	5 (2.6)
Upper stomach pain	33 (9.4)	–	12 (4.9)	0	23 (12.0)	2 (1.0)
Constipation	54 (15.4)	0	27 (10.9)	0	42 (21.9)	0
General symptoms [n (%)]						
Tiredness	110 (31.4)	4 (1.1)	91 (36.8)	11 (4.5)	55 (28.6)	4 (2.1
Weakness	61 (17.4)	5 (1.4)	47 (19.0)	5 (2.0)	35 (18.2)	3 (1.6)
Fever	193 (55.1)	16 (4.6)	71 (28.7)	3 (1.2)	35 (18.2)	7 (3.6)
Oedema/peripheral oedema	48 (13.7)	1 (0.3)	34 (13.8)	0	3 (1.6)	0
Headache	112 (32.0)	4 (1.1)	44 (13.8)	1 (0.4)	42 (21.8)	3 (1.6)
Vertigo	34 (9.7)	1 (0.3)	15 (6.1)	0	24 (12.5)	3 (1.6)
Abnormalities in laboratory results during BRAFi/MEKi treatment [n (%)]						
Increased ALT concentration	49 (14.0)	9 (2.6)	65 (26.3)	28 (11.3)	21 (10.9)	10 (5.2)
Increased AST concentration	42 (12.0)	5 (1.4)	60 (24.3)	22 (8.9)	16 (8.3)	4 (2.1)
Increased GGTP concentration	38 (10.9)	19 (5.4)	54 (21.9)	36 (14.6)	29 (15.1)	18 (9.4)

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Table 1. cont. Frequency of adverse events in combined therapy, which occurred in key clinical trials comparing BRAFi/MEKi combinations with vemurafenib [8]

Combination	Dabrafenib + trametinib		Vemurafenib + cobimetinib		Encorafenib + binimetinib	
Increased ALP concentration	26 (7.4)	7 (2.0)	42 (17.0)	12 (4.9)	16 (8.3)	1 (0.5)
Increased CPK concentration	10 (2.9)	6 (1.7)	87 (35.2)	30 (12.1)	44 (22.9)	13 (6.8)
Increased creatinine concentration	15 (4.3)	0	37 (15.0)	3 (1.2)	12 (6.3)	2 (1.0)
Increased lipase concentration	–	–	9 (3.6)	8 (3.2)	4 (2.1)	3 (1.6)
Hyperglycaemia	17 (4.9)	8 (3.2)	8 (3.2)	1 (0.4)	9 (4.7)	4 (2.1)
Hyponatraemia	16 (4.6)	15 (4.3)	13 (5.3)	7 (2.8)	2 (1.0)	1 (0.5)
Anaemia	26 (7.4)	7 (2.0)	39 (15.8)	4 (1.6)	29 (15.1)	8 (4.2)
Neutropenia	32 (9.1)	17 (4.9)	3 (1.2)	0	5 (2.6)	2 (1.0)
Undesirable effects linked to the musculoskeletal system [n (%)]						
Joint pain	93 (26.6)	3 (0.9)	94 (38.1)	6 (2.4)	49 (25.5)	1 (0.5)
Pain in extremities	45 (12.9)	4 (1.1)	29 (11.7)	3 (1.2)	21 (10.9)	2 (1.0)
Muscle pain	66 (18.8)	0	37 (15.0)	4 (0.4)	26 (13.5)	0
Cardiovascular events [n (%)]						
QT prolongation (EKG)	5 (1.4)	2 (0.6)	11 (4.5)	3 (1.2)	0	0
cardiac ejection fraction decrease	29 (8.3)	13 (3.7)	29 (11.7)	5 (2.0)	11 (5.7)	2 (1.0)
Hypertension	103 (29.4)	54 (15.4)	39 (15.8)	15 (6.1)	21 (10.9)	11 (5.7)
Eye complications [n (%)]						
Blurred vision	17 (4.9)	0	28 (11.3)	0	30 (15.6)	0
Central serous chorioretinopathy	2 (0.6)	0	32 (13.0)	2 (0.8)	5 (2.6)	2 (1.0)
Retinal detachment	–	–	22 (8.9)	5 (2.0)	15 (7.8)	1 (0.5)
Lung complications [n (%)]						
Cough	77 (22.0)	0	23 (9.3)	0	16 (8.3)	1 (0.5)
Pneumonia	2 (0.6)	0	6 (2.4)	3 (1.2)	3 (1.2)	3 (1.6)
Embolism	7 (2.0)	7 (2.0)	2 (0.8)	2 (0.8)	6 (3.1)	2 (1.0)
Kidney-derived complications [n (%)]						
Acute kidney injury	4 (1.1)	4 (1.1)	7 (2.8)	3 (1.2)	3 (1.6)	2 (1.0)
Dehydration	15 (4.3)	6 (1.7)	11 (4.5)	5 (2.0)	11 (4.5)	5 (2.0)

for a certain time (30–32%), dose reduction (13–14%), or stopping the drugs (2–3%) [8, 11].

Undesirable gastrointestinal tract reactions (nausea, vomiting, and diarrhoea)

The frequency of nausea was similar during treatment with encorafenib and binimetinib (41%), encorafenib in monotherapy (39%), and vemurafenib in monotherapy (34%). In the group treated using the drug combination grade 1 nausea was observed in 24% patients, grade 2 in 15%, and grade 3 in 2% [5].

Vomiting was more characteristic for the group treated with encorafenib in combination and in monotherapy (respectively, 30% and 27%), and in the group receiving vemurafenib vomiting was reported in 16% of cases. In the group receiving encorafenib together with binimetinib, 18% had grade 1 vomiting, 10% grade 2, and 2% grade 3 [5].

Diarrhoea was dominant in persons treated with encorafenib in combination with binimetinib (36%) and vemurafenib in monotherapy (34%) but only in 14% of patients receiving encorafenib in monotherapy. In patients treated using the combination in general, grade 1 diarrhoea was reported in 24%, and less frequently grade 2 (10%), 3 (2%), and 4 (0.5%) [5].

The above undesirable gastrointestinal tract effects required a dose modification. In the branch with the combination in 8% patients with nausea, 7% with vomiting, and 4% with diarrhoea, and in 1% diarrhoea was the reason for stopping treatment. The median time from start of treatment to the first occurrence of symptoms was, in the case of nausea, 29 days (1–614 days), vomiting — 57 days (1–607 days), and diarrhoea — 29 days (1–534 days) [5].

Table 2. Adverse events of encorafenib and binimetinib in the COLUMBUS trial [5]

Adverse event (regardless of the grade of toxicity)	Median time to occurrence of adverse events in days (time interval)	Stopping treatment because of adverse events (%)	Dose reduction (%)
Nausea	29 (1–614)	0	8
Diarrhoea	29 (1–534)	1	4
Central serous retinopathy	38 (1–532)	0	6
Vomiting	57 (1–607)	0	7
Hyperkeratosis	77 (1–408)	0	2
Hypersensitivity to light	84 (1–677)	0	1
Fever	85 (2–545)	< 1	4
Joint pain	85 (1–708)	0	2
Left ventricle dysfunction	109 (1–648)	0	6

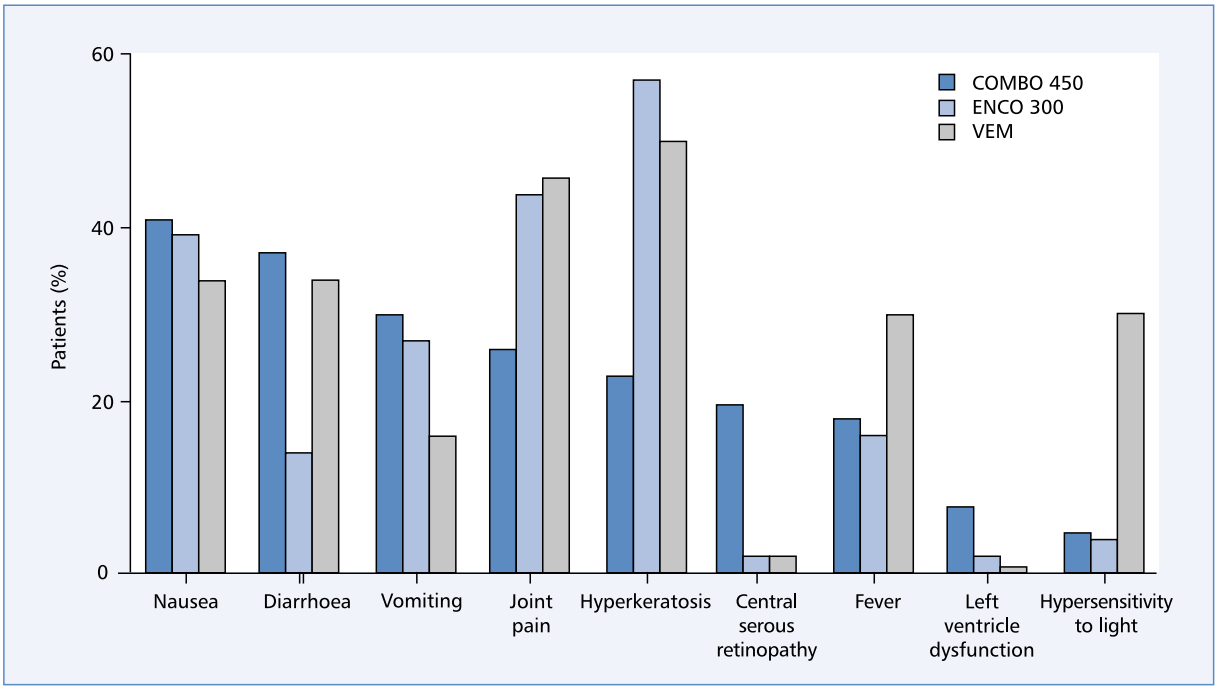

Figure 1. Selected adverse events occurring in patients (of all grades according to CTCAE) in any analysed group; COMBO 450 (450 mg encorafenib once a day plus 45 mg binimetinib twice a day); ENCO 300 (300 mg encorafenib once a day); VEM (960 mg vemurafenib twice a day) [5]

Joint pain

The frequency of occurrence of joint pain was lower in the case of encorafenib with binimetinib (26%), encorafenib in monotherapy (44%), and vemurafenib in monotherapy (46%). The median time from the moment of initiating combined therapy to the first appearance of symptoms was 85 days (1–708 days), and serious joint complications were rare (1% at grade 3). None of the patients required cessation of the therapy or reduction of the dose of drugs for this reason [5].

Hyperkeratosis

The frequency of hyperkeratosis occurrence was lower in the case of encorafenib and binimetinib (23%) than for encorafenib in monotherapy (57%) or vemurafenib in monotherapy (49%). The median time from the moment of initiating combined therapy to the first appearance of symptoms was 77 days (1–408 days). In 2% patients a reduction in drug dose was required, but in no case was treatment interrupted for this reason [5].

Hypersensitivity to light

The frequency of occurrence of hypersensitivity to light in the COLUMBUS trial was lower in the case of encorafenib and binimetinib (5%) and encorafenib (4%) in comparison with vemurafenib (30%). Median time from the moment of initiating combined therapy to the first appearance of symptoms was 84 days (1–677 days). Treatment was not interrupted for this reason in any of the patients, but one patient in the combined therapy group required a dose reduction [5, 8]. For comparison, hypersensitivity to light for vemurafenib and cobimetinib was often recurrent and long-term, which is indubitably related to the pharmacokinetic profile of the drugs [12].

Central serous retinopathy

Central serous retinopathy in the COLUMBUS trial was more frequent in patients treated with encorafenib and binimetinib (20%) in comparison with patients receiving encorafenib (2%) or vemurafenib (2%) in monotherapy. The median time from the moment of initiating combined therapy to the first appearance of symptoms was 38 days (1–532 days). In patients receiving the combination of drugs, grade 1 adverse effects (asymptomatic form) occurred in 12%, grade 2 in 5%, and grade 3 in 3%. In 6% of patients treated with encorafenib and binimetinib, the treatment required a periodic interruption and then a dose reduction, but in no patients was treatment stopped for this reason [5]. In general, central serous retinopathy was a reversible adverse effect. Most patients in whom it developed did not require a pharmacological intervention; however, topically used nonsteroidal anti-inflammatory drugs or carbonic anhydrase inhibitors can be useful in symptomatic treatment [8].

Left ventricle dysfunction (LVD) and other cardiovascular dysfunctions

Left ventricle dysfunction in the COLUMBUS trial was more commonly reported for encorafenib and binimetinib (8%) than for encorafenib in monotherapy (2%) or vemurafenib in monotherapy (1%). Median time from the moment of initiating combined therapy to the first appearance of symptoms was 109 days (1–648 days). Six per cent of patients receiving combined therapy required a periodic interruption of therapy with a subsequent dose reduction, but in no patients was treatment stopped for this reason. Left ventricle dysfunction was in general reversible [5].

In general, QT elongation during treatment is due to BRAFi — the phenomenon was observed in 3–7% patients treated with vemurafenib in monotherapy and in 2% treated with vemurafenib in combination with cobimetinib. QT elongation on this scale was not observed during therapy with dabrafenib or encorafenib, which is related to the chemical structure; these drugs contain an additional fluoridated phenyl ring. It is worth noting that the effect on QT elongation may be due to water-electrolyte perturbations (e.g. in the course of diarrhoea or using other drugs, e.g. proton pump inhibitors and fluoroquinolones). It is important that the EKG be evaluated before initiating treatment, and then every month for the first three months of inhibitor therapy, and then every 12 weeks. Treatment should be stopped when QTc attains a value of > 500 ms or increases by > 60 ms in relation to the initial value [8].

A decrease of the left ventricular ejection fraction ≥ grade 3 according to CTCAE (i.e. when the left ventricular ejection fraction is < 40% or is decreased by > 20% in relation to the initial value) was observed in 4% patients treated with dabrafenib and trametinib, in 2% of those treated with vemurafenib and cobimetinib, and in 1% of those treated with encorafenib and binimetinib. Patients with cardiovascular diseases in their history should be prudently qualified for treatment with BRAF and MEK inhibitors, and during treatment the left ventricular ejection fraction, the troponin level, NT-proBNP, and CPK should be monitored. A decrease in the cardiac ejection fraction by > 10% is a reason for interrupting treatment, and > 20% for stopping it. In symptomatic patients, introducing a beta-blocker can be considered [8].

Hypertension can also be caused by BRAFi and MEKi. During treatment with dabrafenib and trametinib this problem concerns 29% patients, vemurafenib and cobimetinib 16%, and encorafenib and binimetinib 11%. In this case, hypotensive treatment should be initiated according to the guidelines in force [8].

Recommendations concerning procedures in the case of clinically significant adverse effects of BRAFi + MEKi therapy are presented in Table 3 [8].

Table 3. Recommended actions for selected adverse effects of BRAFi MEKi therapy [8]

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Dermatological complications				
Rash	Hydrating creams, continuation of treatment with inhibitors	Topical corticosteroids (in case of maculopapular rash), topical antibiotics (for papular rash), continuation of treatment with inhibitors	Dermatological consultation, reduction of inhibitor doses	Termination of treatment, hospitalization, if e.g. Stevens-Johnson syndrome occurs, toxic epidermal necrolysis
Hypersensitivity to light	Patient education, UV50 protective creams, protection from sun, topical glucocorticosteroids; continuation of treatment with inhibitors	As for grade 1	Dermatological consultation, reduction of inhibitor doses	Dermatological consultation, stopping treatment with inhibitors considered
Hand and foot keratosis	Patient education, urea creams, topical glucocorticosteroids; continuation of treatment with inhibitors	As for grade 1	Dermatological consultation, reduction of inhibitor doses; stopping treatment with inhibitors considered	This adverse effect has not been reported at grade 4
Gastrointestinal complications				
Diarrhoea	Loperamide/octreotide; continuation of treatment with inhibitors	As for grade 1, reduction of inhibitor dose recommended	As for grade 1, inhibitor dose reduction required	Stopping treatment with inhibitors considered
Nausea and vomiting	Pharmacological prophylaxis (available anti-emetic drugs, corticosteroids); continuation of treatment with inhibitors	As for grade 1, dose reduction can be considered	As for grade 1, inhibitor dose reduction required	Stopping treatment with inhibitors considered
Hepatotoxicity	Continuation of treatment with inhibitors	Dose reduction can be considered	Hepatologist consultation recommended; inhibitor dose reduction required	Stopping treatment with inhibitors considered
General symptoms				
Fever	Antipyretic drugs, corticosteroids, interruption of inhibitor treatment if > 38.5°C	As for grade 1, reduction of inhibitor dose recommended especially in case of recurring fever	inhibitor dose reduction required	Stopping treatment with inhibitors considered
Adverse events in the musculoskeletal system				
Joint pain	NSAIDs, continuation of treatment with inhibitors	As for grade 1, dose reduction can be considered	Rheumatologist consultation, inhibitor dose reduction required; stopping treatment with inhibitors considered	This adverse effect has not been reported at grade 4
Muscle pain	Continuation of treatment with inhibitors	As for grade 1, dose reduction can be considered	Rheumatologist consultation, inhibitor dose reduction required; stopping treatment with inhibitors considered	This adverse effect has not been reported at grade 4
Cardiovascular complications				
Arterial hypertension	Self-control, hypotensive treatment according to standards in force, continuation of treatment with inhibitors	As for grade 1, dose reduction can be considered	As for grade 1, inhibitor dose reduction required	Stopping treatment with inhibitors considered

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Table 3. cont. Recommended actions for selected adverse effects of BRAFi MEKi therapy [8]

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Left ventricle dysfunction	This adverse effect has not been reported at grade 1	Cardiologist consultation; dose reduction can be considered	Cardiologist consultation, inhibitor dose reduction required or stopping treatment	Cardiologist consultation, stop treatment with inhibitors
QT prolongation	Modification of cardiological treatment, equilibration of hydro-electrolyte perturbations, continuation of treatment with inhibitors	Cardiologist consultation; dose reduction can be considered	Cardiologist consultation, inhibitor dose reduction required or stopping treatment	Cardiologist consultation, stop treatment with inhibitors
Eye complications				
Central serous retinopathy	continuation of treatment with inhibitors	Dose reduction can be considered	Ophthalmologist consultation, inhibitor dose reduction required	Ophthalmologist consultation, stopping treatment with inhibitors considered
Kidney derived complications				
Acute kidney damage with increase in creatinine	Continuation of treatment with inhibitors	Irrigation, exclusion of other causes, dose reduction can be considered	Nephrologist consultation, inhibitor dose reduction required	Nephrologist consultation, stop treatment with inhibitors
Lung complications				
Pneumonia	Continuation of treatment with inhibitors	If symptomatic, corticosteroids, dose reduction can be considered	Pulmonologist consultation, inhibitor dose reduction required or stopping treatment	Pulmonologist consultation, stop treatment with inhibitors

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