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Tolerability of BRAF/MEK inhibitor combinations: adverse event evaluation and management

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ABSTRACT

The inhibition of the mitogen-activated protein kinases signalling pathway through combined use of BRAF and MEK inhibitors (BRAFi+MEKi) represents an established therapeutic option in patients with *BRAF*-mutated, advanced melanoma. These efficient therapies are well tolerated with mostly moderate and reversible side effects and a discontinuation rate due to adverse events of 11.5%–15.7%. Median duration of therapy ranges between 8.8 and 11.7 months. Based on data from confirmatory trials, safety profiles of three BRAFi+MEKi combinations were reviewed, that is, dabrafenib plus trametinib, vemurafenib plus cobimetinib and encorafenib plus binimetinib. Many adverse events are class effects, such as cutaneous, gastrointestinal, ocular, cardiac and musculoskeletal events; some adverse events are substance associated. Fever (dabrafenib) and photosensitivity (vemurafenib) are the most common and clinically prominent examples. Other adverse events are less frequent and the association to one substance is less strong such as anaemia, facial paresis (encorafenib), neutropenia (dabrafenib), skin rash, QTc prolongation and increased liver function tests (vemurafenib). This narrative review provides recommendations for monitoring, adverse event evaluation and management focusing on the clinically relevant side effects of the three regimens.

INTRODUCTION

Combination therapy with BRAF plus MEK inhibitors (BRAFi+MEKi) offers an effective therapy in *BRAF*-mutated metastatic[1–6] and, for adjuvant therapy, in *BRAF*-mutated stage III melanoma.[7]

Investigator-assessed response rates in *BRAF*-mutated, metastatic melanoma were 64%–67% for dabrafenib+trametinib (D+T),[2 3] 68% for vemurafenib+cobimetinib (V+C)[5] and 75% for encorafenib+binimetinib (E+B)[6]; landmark survival analyses showed 2-year overall survival rates of 53% for D+T,[8] 48% for V+C[9] and 58% for E+B.[10] However, direct comparison of these findings cannot be made since the trials show differences in patient populations; for example, for V+C, a significantly higher number of patients with elevated lactate dehydrogenase levels was included.[11]

Side effects occurring in all three BRAFi+MEKi combinations were assessed during the confirmatory clinical trials.[1–6] Some events can be attributed to BRAFi adverse reactions[12–15] and some to MEKi adverse reactions.[16–19] Class effects of MEKi include the induction of a papulopustular exanthema in almost all treated patients, neuroretinal detachment, muscular problems, hypertension and ventricular ejection fraction decrease. Certain side effects are drug associated and may also occur with the respective combination; examples comprise phototoxicity,[14 15 20 21] fever[12 22] or transient facial paresis.[23]

With extensive adverse event (AE) data sets for E+B becoming publicly available now,[6] the safety profiles of D+T, V+C and E+B are reviewed here with recommendations for monitoring, evaluation and management of the most common or most critical AE.

METHODS AND MATERIALS

The tolerability of the three combination regimens D+T, V+C and E+B is described here by following safety parameters: (1) AE frequencies (all grades and grade 3–4); (2) selected AEs of special interest; (3) serious AE rates; (4) deaths that occurred within 90 days after end of treatment and that are considered 'related' or 'possibly related' to study treatment and (5) dose reduction, dose interruption and dose discontinuation rates in relation to AEs of any causality.

Event rates for the three combinations were extracted from reports of the pivotal, confirmative phase III trials COMBI-V, COMBI-D, coBRIM and COLUMBUS (Part I); rates were determined by the common terminology criteria for AEs of the US National Cancer Institute, V.4.0. A recently published indirect

treatment comparison of D+T versus V+C in previously untreated patients with melanoma provided methodical guidance and updated safety data for the COMBI-V trial[24]; the comparison focused exclusively on trials with vemurafenib (dose regimen 960 mg twice daily) used as a control arm for null-hypothesis testing.

All incidence variables for tolerability were collected from publicly available data sets. Recent data sets were used in this narrative review to compile AE frequency, considering the cut-off dates for safety analyses, length of AE observation and proportion of patients still under therapy (see online supplementary file 1 for additional information). Follow-up times for AE data sets analysed in our paper, calculated as period from day of last-patient-included until safety-data cut-off-date, were 19.8 months (D+T),[24 25] 18.5 months (V+C)[9 26] and 16.5 months (E+B).[6]

This retrospective, non-experimental analysis of anonymised, pooled patient data did not require institutional review board approval. Standard recommendations to enhance the quality of evidence-based judgements were followed as previously described.[27 28]

Pharmacological drug profiles

The various BRAFi and MEKi differ in kinase-binding properties, structural and pharmacodynamic characteristics. These parameters influence the inhibitory potency towards the V600-mutated BRAF kinase and determine off-target effects.[29]

For the predominant $BRAF^{V600E}$-mutant kinase, the half maximal inhibitory concentration (IC_{50})—a measure of the potency of a drug to inhibit a specific biological or biochemical function—is 0.65 nM for dabrafenib, 10 nM for vemurafenib and 0.35 nM for encorafenib. All three BRAFi were also active against other BRAF mutations as well as against wild-type BRAF. Encorafenib inhibited most cell lines at an IC_{50} of <40 nmol/L; slightly higher concentrations of dabrafenib (<100 nmol/L), but significantly higher concentrations of vemurafenib (<1000 nmol/L) were required in the same assay to inhibit proliferation of most cell lines with BRAF mutations.[23]

The dissociation half-life ($t_{½diss}$), a measure describing target inhibition and its durability, is relevant to determine drug-dosing intervals. In vitro investigations on drug–receptor interactions indicated that $t_{½diss}$ for encorafenib is with >30 hour considerably longer than for dabrafenib (2 hour) or vemurafenib (0.5 hour), resulting in longer lasting pharmacodynamic target inhibition of encorafenib.[23]

For the MEKi trametinib, IC_{50} values for in vitro inhibition of MEK1 and MEK2 range between 0.7 and 0.9 nM.[30] The IC_{50} of cobimetinib for MEK1 is with 0.95 nM much lower than for MEK2 (199 nM).[30] In target inhibitory assays, binimetinib was a potent inhibitor of MEK1 and MEK2 with an enzyme IC_{50} of 12–46 nM.[30]

Bioavailability, a measure how much of the administered drug reaches systemic circulation, was 95% and 85% for BRAFi dabrafenib and encorafenib, respectively.[23 31–33] For vemurafenib with its low solubility and permeability, it is unknown.[20] For MEKi trametinib, cobimetinib and binimetinib, bioavailability was 72%,[34 35] 46%[18] and 50%,[36] respectively.

Further pharmacokinetic properties of the BRAFi and MEKi, as determined in their early clinical trials,[18 20 23 34–36] are outlined in figure 1. Due to their differing bioavailability and pharmacokinetics, drug doses and administration schedules vary: 150 mg dabrafenib are administered twice daily 1 hour before or 2 hour after the morning and evening meal (ie, 75 mg capsules 2-0-2), vemurafenib twice daily (960 mg per dose; 240 mg tablets 4-0-4), and encorafenib once daily in the morning or evening independent of food intake (450 mg; 75 mg capsules 6-0-0 or 0-0-6).

Administration of trametinib (2 mg; 2 mg tablets 1-0-0) as well as of cobimetinib (60 mg; 20 mg tablets 3-0-0) is once daily, whereas binimetinib is taken twice daily (45 mg per dose; 15 mg tablets 3-0-3). In combination, D+T and E+B are administered continuously. V+C is administered in combination for 21 days plus 7 days rest for cobimetinib.[4]

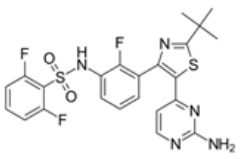
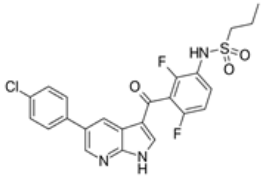
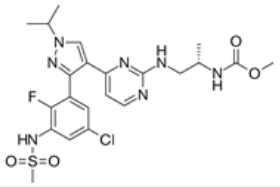
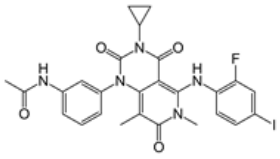
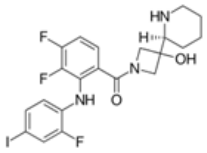
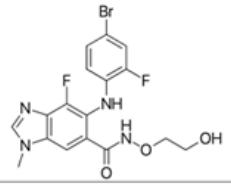
Toxicity profiles of BRAFi and MEKi monotherapies

For dabrafenib, treatment-related fever has been identified in 20% of patients in its first-in-human phase I trial[22]; no dose–response correlation was noted for fever of grade 2 or higher in the monotherapy trials, but pharmacokinetic analyses conducted in the context of the BRAFi+MEKi combination studies showed a possible association between fever and exposure to the hydroxy-dabrafenib metabolite and, to a lesser extent, to dabrafenib.[3] Common toxicities included cutaneous side effects, arthralgia, fatigue and headache.[13]

Most treatment-related side effects of vemurafenib appeared to be proportional to dose and exposure of the drug[20]; the photosensitivity induced by vemurafenib is considered to be a property of the chemical structure of the drug, not related to its BRAF-inhibiting activity.[22] Common side effects in early monotherapy trials were arthralgia, nausea, fatigue, rash, cutaneous squamous-cell carcinoma, pruritus and palmar–plantar dysesthesia.[20]

Most frequent drug-related AEs occurring with encorafenib monotherapy included myalgia, nausea, palmoplantar erythrodysesthesia, arthralgia, alopecia and hyperkeratosis. Transient Bell's palsy, the most common disorder affecting a single nerve and associated with facial nerve weakness/paralysis, was reported in 8% of patients treated with encorafenib, whereas it has rarely been reported in association with other BRAFi.[33]

Trametinib showed an early onset of dose-limiting toxic effects, as observed in trametinib's first-in-human trial including 206 patients[34] with two cases of rash, one case of diarrhoea and three cases of central serous retinopathy. As two of the three ocular toxicity events arose either 1 day after a loading dose or within days of administration of the highest once-daily dose, this treatment-related effect was thought to be potentially related to the C_{max} of trametinib.[34] Similarly, a reported papulopustular

	Dabrafenib / Trametinib	Vemurafenib / Cobimetinib	Encorafenib / Binimetinib
BRAF Inhibitors **Dab.** (GSK2118436) / **Vem.** (PLX4032,RG7204) / **Enc.** (LGX818)			
	RP2D: **150 mg td** (MTD not reached) * BCS class: II (high permeability, low solubility) Food effect: Intake 1h prior or 2 h after meal Absorption (t_{max}): **1.9 h** Time to steady-state ($t_{max,ss}$): **14 d** $AUC_{0-24,ss}$: **4.3 h*µg/mL** (38 %CV_b) $C_{max,ss}$: **1478 ng/mL** (37 %CV_b) Clearance (CL/F): **17.3 L/h** (nc) Elimination half-life (t½): **8.4 h** (nc)	RP2D: **960 mg td** (=MTD) BCS class: IV (low permeability, low solubility) Food effect: none (Intake with/without food) Absorption (t_{max}): ~**4 h** Time to steady-state ($t_{max,ss}$): **15-22 d** $AUC_{0-8,ss}$: **380.2 h*µg/mL** (38 %CV_b) $C_{max,ss}$: **56,700 ng/mL** (38 %CV_b) Clearance (CL/F): **1.2 L/h** (32 CV_b%) Elimin. half-life (t½): **56 h** [30-120]	RP2D: **300 mg od** (MTD: 450 mg od) BCS class: *nr* Food effect: None (Intake with/without food) Absorption (t_{max}): **2.0 h** Time to steady-state ($t_{max,ss}$): **15 d** $AUC_{0-24,ss}$: **12.3 h*µg/mL** (med.) $C_{max,ss}$: **3100 ng/mL** (med.) Clearance (CL/F): **24.4 L/h** (med.) Elimination half-life (t½):**6.3 h** [3.7-8.1]
MEK Inhibitors **Tra.** (GSK1210212) / **Cob.** (RG7420) / **Bin.** (MEK162)			
	RP2D: **2 mg od** (MTD: 3 mg od) BCS class: II (high permeability, low solubility) Food effect: Intake 1h prior or 2 h after meal Absorption (t_{max}): **1.5 h** Time to steady-state ($t_{max,ss}$): **15 d** $AUC_{0-24,ss}$: **0.4 h*µg/mL** (22 %CV_b) $C_{max,ss}$: **22 ng/mL** (28 %CV_b) Clearance (CL/F): **5.4 L/h** (nc) Elimination half-life (t½): **90 h** [58-183]	RP2D: **60 mg od** (d1-21 q4w) (=MTD) BCS class I: (high permeability, high solubility) Food effect: none (Intake with/without food) Absorption (t_{max}): **2.4 h** Time to steady-state ($t_{max,ss}$): **10 d** $AUC_{0-24,ss}$: **4.3 h*µg/mL** (61 %CV_b) $C_{max,ss}$: **273 ng/mL** (60 CV_b%) Clearance (CL/F): **13.8 L/h** (61% CV) Elimination half-life (t½): **44 h** [23-69]	RP2D: **45 mg td** (MTD: 60 mg td) BCS class: *nr* Food effect: none (Intake with/without food) Absorption (t_{max}): **2.0 h** (1.5 h at 60 mg td) Time to steady-state ($t_{max,ss}$): **15 d** $AUC_{0-8,ss}$: **1.5 h*µg/mL** (nc) $C_{max,ss}$: **273 ng/mL** (65 %CV_b) Clearance (CL/F): *nr* Elimination half-life (t½): **8.7 h** (nc)

* no-dose-limiting toxicity recorded at 300 mg td

Figure 1 Structural and population pharmacokinetic properties (single drug) of BRAF indicator dabrafenib, vemurafenib and encorafenib and of MEK indicator trametinib, cobimetinib and binimetinib. AR, accumulation ratio; AUC 0–24, area under the curve for 0–24 h (AUC 0–8 : 0-8 h); BCS, biopharmaceuticsclassification system; C max, maximum concentration; C 24, concentration after 24 h; d, days; h, hours; MTD,maximum tolerated dose; od, once daily; RP2D, recommended phase 2 dose; t 1/2 eff, effective half-life,calculated as –0.693*tau/(ln[1–{1/AR}]); td, twice daily; t max, time taken to reach maximum concentration,reported as median. In brackets: (%CV b), between-subject coefficient of variation; (nc), not calculated; (nr),not reported; […], range. All reported values are means, if not indicated otherwise (i.e. median).

exanthema adverse reaction emerging after cessation of combined D+T treatment was proposed to be associated with trametinib's long half-life[37] (figure 1).

Cobimetinib's most frequent AEs attributed in its phase I monotherapy trial were diarrhoea, rash, fatigue, oedema, nausea and vomiting.[18]

Dose-limiting toxicities of binimetinib in early monotherapy trials were single events of therapy-resistant papulopustular rash and of central serous-like retinopathy, respectively. Other frequent treatment-related AEs included gastrointestinal (GI) (diarrhoea, nausea) and skin disorder as well as peripheral oedema, increased creatine phosphokinase (CPK) and retinal disorders.[38]

Toxicity profile of BRAFi+MEKi combinations

Overall AE and serious AE frequencies for the three combinations D+T, V+C and E+B and the respective median drug exposure times are displayed in table 1. Although comparison across trials has its limitations, that is, with respect to different methodological AE evaluation across trials, AE rates in the respective vemurafenib comparator arms are nearly identical.[6 9 24] AEs of any grade occurred in almost all patients treated with the combination therapy. In patients treated with a BRAFi+MEKi, grade 3–4 AEs occurred in 46%–56% for D+T (COMBI-D, COMBI-V), 69% for V+C (coBRIM) and 58% for E+B (COLUMBUS, Part I).

Median duration of therapy ranged between 10.0 and 11.0 months for D+T, 8.8 months for V+C and 11.7 months for E+B, with median dose intensities ranging between 94% and 100% for all substances.

The detailed AE frequencies of D+T (COMBI-V), V+C (coBRIM) and E+B (COLUMBUS Part I) for relevant organ systems are listed in table 2. To facilitate the analysis and interpretation of the data, AE frequencies for the combination regimen versus frequencies of the respective vemurafenib monotherapy arms of each trial[6 9 24] were compared: the respective shifts, expressed as an increase or decrease in BRAFi+MEKi AE rates compared with vemurafenib, are displayed in figure 2.

Table 1 Overall frequencies of adverse events in the safety populations of the pivotal clinical trials and median drug exposure times and rates

Combination regimen of interest	**Dabrafenib+Trametinib (D+T)**				**Vemurafenib+Cobimetinib (V+C)**		**Encorafenib+Binimetinib (E+B)**		
Date of (safety) analysis	**13 Mar 2015**[24 25]		**12 Jan 2015**[2]		**19 Sep 2014**[24]		**19 May 2016**[6]		
Study	COMBI-V		COMBI-D		coBRIM		COLUMBUS Part 1		
Arms	D+T	V	D+T	D+placebo	V+C	V+placebo	E+B	V	E
N° pts (ITT) rand (N° safety population)	352 (350)	352 (349)	211 (209)	212 (211)	247 (247)	248 (246)	192 (192)	191 (186)	194 (192)
Daily dose (mg)	300/2	1920	300/2	300	1920/60	1920	450/90	1920	300
Events (frequencies)									
AE (all grades, any causality) (%)	345 (98.6)	345 (98.9)	203 (97.1)	205 (97.2)	244 (98.8)	240 (97.6)	188 (97.9)	185 (99.5)	191 (99.5)
AE (°3–4) (%)	195 (55.7)	228 (65.3)	95 (45.5)	106 (50.2)	171 (69.2)	143 (58.1)	111 (57.8)	118 (63.4)	127 (66.1)
AE leading to death ('fatal AE'; (°5)) (%)	4 (1.1)	4 (1.2)	5 (2.4)	1 (0.5)	5 (2.0)	3 (1.2)	3 (1.7)	2 (1.1)	2 (1.0)
AE leading to discontinuation (%)	55 (15.7)	48 (13.8)	24 (11.5)	14 (6.6)	37 (15.0)	20 (8.1)	24 (12.5)	31 (16.7)	27 (14.1)
AE leading to dose reduction (%)	192 (54.9)	197 (56.4)	59 (28.2)	29 (13.7)	110 (44.5)	87 (35.4)	22 (11.5)	42 (22.6)	52 (27.1)
AE leading to dose interruption (%)			118 (56.5)	78 (37.0)			88 (45.8)	98 (52.7)	122 (63.5)
SAE (all grades, any causality) (%)	151 (43.1)	136 (39.0)	88 (42.1)	78 (37.0)	85 (34.4)	64 (26.0)	66 (34.4)	69 (37.1)	65 (33.9)
Dose exposure rates/times (months)									
Median duration of therapy (range)	10.0 (0–21)	6.0 (0–18)	11.0 (0–30)	8.0 (0–32)	8.8 (0–18)	5.7 (0–17)	11.7 (0–27)	6.2 (0–28)	7.2 (0–26)
Median dose intensity (in %)	97.3%+100%	96.1%	98.2%+100%	99.9%+*100%*	94.4%+96.6%	96.7%+*99.0%*	100%+99.6%	94.5%	86.2%

AE, adverse events; B, binimetinib; C, cobimetinib; D, dabrafenib; E, encorafenib; ITT, intention-to-treat; SAE, serious adverse event; T, trametinib; V, vemurafenib; pts rand., patients randomized.

Table 2 Frequencies of AE of combination therapy arms, as observed in the safety population of pivotal clinical trials comparing BRAFi +MEKi combinations versus vemurafenib[6 9 24]

Combination regimen of interest	Dabrafenib+Trametinib (D+T)		Vemurafenib+Cobimetinib (V+C)		Encorafenib+Binimetinib (E+B)	
Data cut-off dates (safety analysis)	13 Mar 2015		30 Sep 2015		19 May 2016	
Median follow-up time	19.8 months		18.5 months		16.6 months	
Study	COMBI-V		coBRIM		COLUMBUS Part 1	
N° pts rand. (intention to treat) (safety population)	352 (350)		247 (247)		192 (192)	
Daily dose (mg)	300/2		1920/60		450/90	
CTC AE grade	**Any**	**3–4**	**Any**	**3–4**	**Any**	**3–4**
Dermatological events, including new skin neoplasms						
Rash*	84 (24.0)	3 (0.9)	101 (40.9)	**13** (5.3)	27 (14.1)	**2** (1.0)
Rash maculopapular	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
Dermatitis acneiform*	23 (6.6)	0	34 (13.8)	6 (2.4)	6 (3.1)	0
Alopecia	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)
Palmoplantar keratoderma	–	–	5 (2.0)	0	17 (8.9)	0
Palmo–plantar erythrodysesthesia*†	14 (4.0)	0	17 (6.9)	0	13 (6.8)	(0)
Actinic 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
Photosensitivity reaction*	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
Keratocanthoma*	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 events						
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)
Abdominal pain	39 (11.1)	1 (0.3)	27 (10.9)	1 (0.4)	32 (16.7)	5 (2.6)
Abdominal pain upper	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 disorders (and symptoms/disorders of central nervous system)						
Fatigue	110 (31.4)	4 (1.1)	91 (36.8)	11 (4.5)	55 (28.6)	4 (2.1)
Asthenia	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)
Peripheral oedema/swelling*‡	*48 (13.7)*	*1 (0.3)*	34 (13.8)	0	3 (1.6%)	0
Headache*	112 (32.0)	*4 (1.1)*	44 (17.8)	1 (0.4)	42 (21.8)	3 (1.6)
Dizziness*	*34 (9.7)*	*1 (0.3)*	15 (6.1)	0	24 (12.5)	3 (1.6)
Investigations/laboratory examinations						
ALT level increased	49 (14.0)	9 (2.6)	65 (26.3)	**28** (11.3)	21 (10.9)	10 (5.2)
AST level increased	42 (12.0)	**5** (1.4)	60 (24.3)	22 (8.9)	16 (8.3)	4 (2.1)

Continued

Table 2 Continued

CTC AE grade	Any	3–4	Any	3–4	Any	3–4
γ-GT level increased	38 (10.9)	19 (5.4)	54 (21.9)	**36** (14.6)	29 (15.1)	18 (9.4)
Blood AP increased	26 (7.4)	7 (2.0)	42 (17.0)	12 (4.9)	16 (8.3)	1 (0.5)
Blood CPK level increased	10 (2.9)	6 (1.7)	87 (35.2)	**30** (12.1)	44 (22.9)	**13** (6.8)
Blood creatinine level increased	15 (4.3)	0	37 (15.0)	**3** (1.2)	12 (6.3)	2 (1.0)
Lipase level increased	–	–	9 (3.6)	**8** (3.2)	4 (2.1)	**3** (1.6)
Hyperglycaemia*	*17 (4.9)*	*8 (2.3)*	8 (3.2)	1 (0.4)	9 (4.7)	4 (2.1)
Hyponatremia*	*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)
Musculoskeletal events						
Arthralgia	93 (26.6)	3 (0.9)	94 (38.1)	6 (2.4)	49 (25.5)	1 (0.5)
Pain in extremity	45 (12.9)	4 (1.1)	29 (11.7)	3 (1.2)	21 (10.9)	2 (1.0)
Myalgia	66 (18.8)	0	37 (15.0)	1 (0.4)	26 (13.5)	0
Cardiovascular events						
QT interval prolongation (ECG)*	5 (1.4)	*2 (0.6)*	11 (4.5)	3 (1.2)	0	0
Ejection fraction decreased*	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)
Ocular events						
Vision blurred	17 (4.9)	0	28 (11.3)	0	30 (15.6)	0
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)
Pulmonary events						
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 (1.6)	3 (1.6)
Pulmonary embolism*	*7 (2.0)*	*7 (2.0)*	2 (0.8)	2 (0.8)	6 (3.1)	**2** (1.0)
Renal events						
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)

Listed are AE with event frequencies (of any grade) ≥10%, and/or with event frequencies (≥2% for grade ≥3 AE) and frequency independent, clinically relevant 'AE of specific interest'.
Values in bold indicates CTC grade 3 and grade 4 toxicity reported; values in italics indicates different data cut-off dates for safety analysis (D+T only).
*D+T: values and frequencies reported at initial safety analysis (14 April 2014) only,[2] extended listings are published in the European Public Assessment Report (EMA/589140/2015, dated 2 Septmber 2015).
†D+T: term 'hand–foot syndrome' was reported, including the terms palmo–plantar erythrodysesthesia, planto–palmar hyperkeratosis and palmoplantar keratoderma.
‡E+B: frequencies for peripheral swelling were reported.
–, not reported; AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CTC, common toxicity criteria; GT, γ-gamma-glutamyl transferase; pts rand., patients randomised.

Remarkably, most cutaneous side effects, particularly secondary neoplasms (cutaneous squamous cell carcinoma and its specific variant keratoacanthoma and skin papilloma), decreased considerably compared with BRAF monotherapy (figure 2); this effect is explained in the literature by the suppression of the paradoxical activation of the mitogen-activated protein kinases (MAPK) pathway in BRAF wild-type cells in various tissues through MEKi coadministration.[39] On the other side, an increase of GI side effects, particularly vomiting, is noted due to the addition of the MEKi. Increases in cardiac and ocular side effects are related to MEKi coadministration as well.

Therapy related, organ class-specific AEs

Dermatological events, secondary skin neoplasms

The most frequent cutaneous side effects are rash, itching, dry skin, hair loss, photosensitivity reaction, keratinocytic proliferation and panniculitis.

Different conditions such as maculopapular exanthema, papulopustular exanthema or even eczema

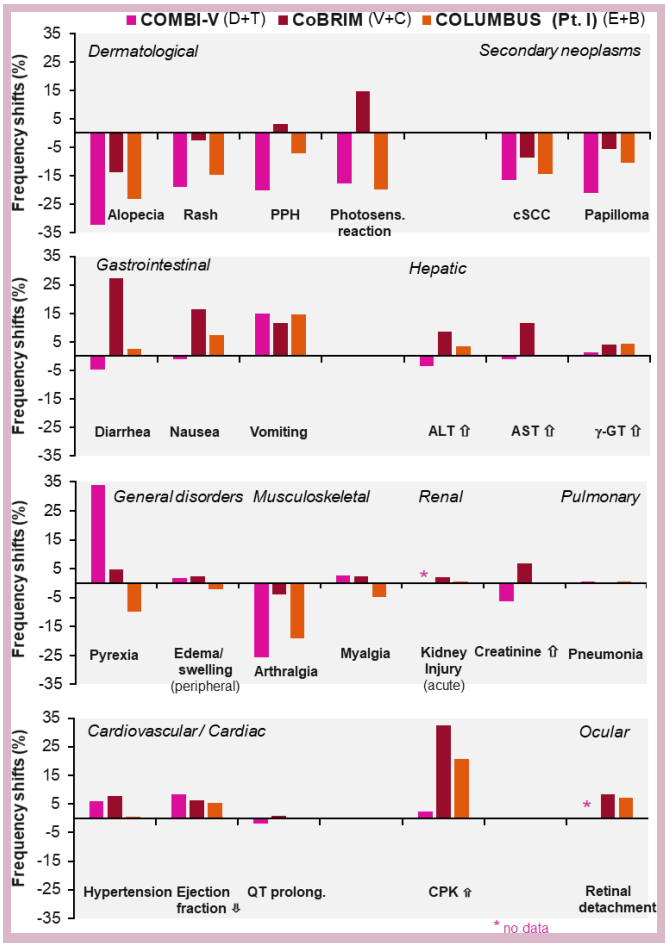


Figure 2 Differences in adverse event frequencies: combination therapies versus vemurafenib monotherapy. CPK, creatine phosphokinase; cSCC, cutaneous squamous cell carcinoma; PPH, palmoplantar hyperkeratosis.

are often summed up by 'rash'; however, a differentiation is desirable to apply the most adequate treatment approach. Rash was most often reported for V+C with 41% and was less common for D+T (24%) and for E+B (14%) (table 2). Although 'rash' is often a low-grade AE, severe and even life-threatening side effects of the skin have been reported, including erythema exsudativum multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, drug-induced hypersensitivity syndrome and acute generalised exanthematous pustulosis.[40]

Dry skin (xerosis cutis) and itching (pruritus) are side effects that occur regularly among all three combinations with a frequency of 10%–20% (table 2). Pruritus is often the result of xerosis cutis.

In 34% of patients treated with V+C, ultraviolet A (UVA)-mediated photosensitivity reactions with erythema, blistering and painful burning were reported, whereas this occurred only in 4% of patients treated with D+T or E+B. Radiosensitivity was observed in patients treated concomitantly with radiotherapy and BRAFi/MEKi, mainly with vemurafenib.[41] Effectiveness does not seem to be reduced by interruption of BRAF therapy during radiotherapy, as shown for vemurafenib.[42]

BRAFi+MEKi therapy associated 'alopecia' generally means diffuse hair loss. Interestingly, curly hairs often found under BRAFi monotherapy are not observed under BRAFi+MEKi therapy.

Keratinocytic proliferations including keratosis pilaris, actinic keratoses, cutaneous squamous cell carcinoma (cSCC), keratoacanthoma and skin papilloma were observed in up to 7% of patients treated with BRAFi+MEKi (table 2). Keratosis pilaris with disseminated small hyperkeratotic follicular papules on the face or proximal extremities was reported in 4%–7% of patients (table 2). With regard to hand–foot syndrome, there is a spectrum of clinical variants: palmoplantar erythrodysesthesia (PPE) with inflammatory and painful lesions not restricted to pressure points and palmoplantar hyperkeratosis (PPH, also called palmoplantar keratoderma) with hyperkeratotic and painful lesions at pressure points. They are also called type I and type II hand–foot syndrome.[43] Within the clinical studies, this was not clearly differentiated (table 2). While encorafenib seems to induce both PPE and PPH more often than vemurafenib or dabrafenib, the BRAFi+MEKi combination therapy is well tolerated: mainly PPH occurs.[44] Frequency of PPH is lowered with D+T and E+B, compared with vemurafenib (figure 2).

D+T, V+C or E+B induce benign acanthotic skin papillomas, keratoacanthomas and well-differentiated cSCC in 2%–7%, 1%–2% and 1%–4% of patients, respectively (table 2); these rates are lower than the AE rates induced by BRAFi monotherapy (figure 2). New primary melanomas were observed in less than 1% of all patients treated with BRAFi+MEKi. Moreover, panniculitis with painful erythematous subcutaneous nodules predominantly located on the extremities and buttocks—which can occur with or without fever, arthralgia or joint swelling—have been described under combined BRAFi+MEKi with unknown frequency.[45]

Cutaneous side effects are usually well treatable and should not immediately lead to dose reduction or discontinuation of therapy. Exanthema, xerosis cutis and pruritus can be successfully treated by regular application of moisturisers containing urea or glycerine or topical application of class II–III glucocorticoids. Severe cases of exanthema require systemic steroids, dose interruptions or permanent discontinuation.

For ultraviolet (315–380 nm: UVA) mediated photosensitivity, strict avoidance of UVA and sun protection with UVA filter-containing sun screen and protective clothing (including hat, sunglasses) is crucial even behind windows since UVA can penetrate the window glass. Sunburn can be treated with topical steroids and possibly by non-steroidal anti-inflammatory drugs (NSAIDs).

Keratosis pilaris and PPH can be treated with creams containing urea or salicylic acid and in cases of inflammation with topical steroids. Patients with PPH should avoid pressure and friction. Panniculitis can be treated symptomatically with non-steroidal anti-inflammatory

drugs (eg, etoricoxib), topical steroids and compression; some severe cases require systemic steroids and temporary dose interruption. Keratoacanthomas, cSCC and new primary melanomas should be surgically removed.

GI events

GI toxicities are commonly seen during therapy with BRAFi+MEKi and include diarrhoea and nausea and vomiting and can be accompanied by abdominal pain and GI bleeding. Frequencies of GI AE are, with shifts, for example, for diarrhoea up to 27%, higher for the combination of BRAFi+MEKi compared with either monotherapy (figure 2). The underlying pathophysiological mechanisms are not completely understood. The MAPK pathway is activated via EGFR in GI normal mucosa and there is evidence that this pathway is a negative regulator of chloride secretion. Inhibitors of the EGFR pathway could therefore increase chloride secretion and thereby induce secretory diarrhoea.[46]

Alternative aetiologies for GI toxicities such as progressive disease or infection (eg, *Clostridium difficile* infection or other bacterial/viral pathogens) need to be ruled out; the time of onset is of diagnostic relevance to assess whether the AE is treatment related. A cytomegalovirus DNA PCR performed in blood can diagnose cytomegalovirus infection or reactivation. For persistent grade 2 diarrhoea, colonoscopy with colonic biopsies can be considered. All grade diarrhoea occurred much more frequently in patients treated with V+C (61%), compared with D+T or E+B (34% and 36%); nausea (36%–41%) and vomiting (26%–31%), however, occurred at similar frequencies (table 2).

Management includes rehydration since vomiting and diarrhoea can lead to dehydration, hypotension and in severe cases to kidney failure. Grades 1 and 2 diarrhoeas may be managed with antidiarrhoeal medications including loperamide and octreotide, oral hydration and electrolyte supplements. In grade ≥3 cases, BRAFi/MEKi therapy should be withheld in addition to symptomatic treatment. Common GI adverse reactions usually resolve within a few days after cessation of treatment. Systemic treatment and prophylaxis of nausea and vomiting should follow established guidelines.

Hepatic AE manifest as asymptomatic increase of liver function tests, mainly aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase, rarely bilirubin. They are very frequent (table 2). The very common frequency of AST and ALT events may be related to the addition of the MEKi (figure 2). Regular laboratory controls are required with treatment interruption in case of elevations of grade 3 or higher. In some cases with grade 2 elevation, specifically with simultaneous elevated bilirubin levels, treatment may be paused earlier. Other causes of acute liver injury such as infection should be ruled out.

General disorders and haematological events

Fever, fatigue and peripheral oedema are very frequent with BRAFi+MEKi therapy. Fever is one of the main symptoms under D+T treatment, occurring in more than half of the patients (table 2) and is more frequent than under BRAFi monotherapy with vemurafenib (21%) or dabrafenib (28%).[3 24] However, the grade ≥3 fever rate remains below 5%. E+B and V+C can also induce fever, but less frequent (ie, in 18%–29% of patients). Fatigue can accompany this AE or may occur independently, with similar frequencies throughout the three combinations (28%–37%).

Fever occurs early after treatment start—mainly within the first 4 weeks.[26 47] A dose interruption of both drugs is recommended if the fever exceeds 38.5°C. The aetiology of BRAFi+MEKi induced fever is still unclear, and an infectious cause should be excluded. No baseline clinical characteristics predict fever, and it is not associated with treatment outcome.[47] The fever can be treated with antipyretics such as ibuprofen and paracetamol and, if not effective, with low-dose corticosteroids. To avoid hypovolaemia with hypotension and possible acute renal failure, sufficient fluid substitution is important. As soon as the fever ceased for at least 24 hours, BRAFi+MEKi therapy can be restarted.[48] Patients experience a median of two events of fever, with 21% of patients having ≥4 events.[47] A dose reduction is recommended if fever recurs. However, clinical experience shows that short 'drug holidays' (about 2–7 days) are much more effective and the full dose can be maintained.[48] In recurrent cases, intermittent treatment might be an option to avoid additional fever events.

Peripheral oedema is a typical side effect of the MEKi (table 2). Mostly extremities are affected, but facial oedema especially of the eye lids is also common. In mild cases, symptomatic treatment with compression therapy and head elevation while sleeping is adequate after exclusion of other causes, for example, hypalbuminaemia or reduced kidney function.

Haematological events occur in the form of disorders in the different cell subsets of the peripheral blood, most frequently anaemia with around 15% for V+C and E+B and 7% for D+T. Severe anaemia occurs in 2.0, 1.6 and 4.2% for D+T, V+C and E+B, respectively. In contrast, D+T induces neutropenia more frequently, followed by E+B and rarely occurring in V+C (table 2). In general, neutropaenia occurs with a late onset (up to 2 months after treatment initiation) and resolves without dose modifications. All other reported differential blood count changes such as thrombocytopenia, lymphopenia and eosinophilia occur with AE frequencies below 5% and are rarely severe.

Musculoskeletal/rheumatic events

Musculoskeletal/rheumatic side effects primarily include arthralgia, myalgia and vasculitis.

Arthralgia—the main musculoskeletal event—is a very common AE associated with BRAF monotherapy. In

combination, incidences of arthralgia were lowered for D+T, V+C and E+B (figure 2): arthralgia of grade 1–2 remains, however, a very common AE (table 2). Grade ≥3 arthralgia events occur at frequencies of 0.5%–2%; drug withdrawal or adjustment may be considered. Arthritis also appears to occur more frequently in BRAF monotherapy compared with combination therapy[9] and can be managed with dose reduction and corticosteroid treatment.[49]

Myalgia is another very common AE, occurring with BRAFi+MEKi in 14%–19% (table 2); frequencies are similar for the different BRAFi (figure 2).

Vasculitis is mainly described in single patients treated with BRAFi as cutaneous side effects in the context of panniculitis,[45 50–53] and as leukocytoclastic vasculitis,[45 54] but also involving the kidney as glomerulonephritis[55 56] and the eye as retinal vasculitis.[57]

For treatment of mild symptoms of arthralgia or myalgia, NSAIDs or low-dose corticosteroids can be applied. For more accentuated musculoskeletal/rheumatic side effects that require intra-articular or high-dose steroids, rheumatologists should be consulted.

Severe AEs, for example, myositis or vasculitic organ-threatening manifestations require moderate to high-dose (1 mg/kg) corticosteroids; BRAFi/MEKi therapy discontinuation can be considered. If symptoms persist, corticosteroid-sparing therapies like leflunomide or methotrexate can be applied. Based on findings from in vitro and in vivo models, in which leflunomide prevents melanoma growth in combination with BRAFi+MEKi,[58] leflunomide might be preferred.

Cardiovascular events

Cardiovascular side effects have been described for BRAFi and MEKi including QT-prolongation, cardiomyopathy with reduced pump function and hypertension. While QT prolongation is mainly an issue in treatment with BRAFi, decreased ejection fraction has been described for MEKi, however, with different frequencies. The MAPK pathway in cardiomyocytes is a protective signalling pathway and its inhibition interferes with intramyocytic repair mechanisms by inhibition of extracellular signal-regulated kinases 1/2.[59] Immunotherapy-mediated subclinical cardiotoxicity or damage induced by radiotherapy may therefore increase the risk for significant left ventricular systolic dysfunction or even heart failure induced by concomitant or subsequent use of BRAFi and MEKi.[60] However, despite fatal events considered to be due to arrhythmias or sudden cardiac death (10/139 in an analysis of the FDA Adverse Event Reporting System database[60 61]), most of the cardiac side effects can be adequately managed and are reversible.

QT prolongation was observed in up to 3%–7% of patients treated with vemurafenib and 2% treated with V+C[5 62] and has been shown to be dose dependent.[63] Grade ≥3 QT interval prolongation occurred in 1% of patients treated with vemurafenib monotherapy or with V+C.[9] Such negative effects on QT prolongation were not seen with dabrafenib or encorafenib, considered to be due to an additional fluorinated phenyl ring.[6 64 65] The MEKi trametinib caused no QT prolongation.[66] Importantly, other factors like electrolyte disturbances, long QT syndrome and concomitant medications can potentiate the AE.

Thus, electrolyte dysbalances, for example, due to diarrhoea, should be corrected (including magnesium) and other QT-prolonging drugs (eg, pantoprazole, ciprofloxacin) omitted.[67] ECG should be assessed before therapy and monthly during the first 3 months, then every 12 weeks; doses should be withheld in case of QTc >500 ms, or more than 60 ms increase from baseline.

It is important to detect left ventricular dysfunction in treatment with BRAFi+MEKi, since it often results in discontinuation of therapy. The degree of left ventricular dysfunction can range from asymptomatic changes, best diagnosed by echocardiographic strain analysis, to severe cardiac failure. Although BRAFi+MEKi were not included in the European Society for Medical Oncology guidelines on cardiotoxicity, the guideline outlines the diagnostic procedures including cardiac MRI and multigated acquisition scans.[68]

Grade ≥3 decrease in ejection fraction (ie, <40% or decrease of >20% from baseline) was reported in 4%, 2% and 1% in D+T, V+C, and E+B, respectively (table 2). Myocardial dysfunction is modified by genetic factors and impaired myocardial function before initiating cancer treatment, arterial hypertension, >65 years of age, body mass index >30 kg/m^2 and radiotherapy increase the risk. The onset of left ventricular dysfunction after application of MEKi or BRAFi+MEKi therapy ranges from 2 weeks to 5 months and 1–13 months, respectively, and resolved in the majority of cases.[61]

Thus, risks and benefits of BRAFi+MEKi therapy should be carefully evaluated in patients with significant heart disease, and hypertension should be controlled before initiation of therapy. Ejection fraction, troponin and the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) should be checked at therapy start. While troponin indicates myocardiac damage and thus represents an early marker, NT-proBNP is associated with myocardial insufficiency and a marker of chronic heart failure. Further controls can be adapted based on risk factors, symptoms and CPK findings. Management includes withholding treatment in case of an ejection fraction reduction of >10%, with rechallenge at a lower dose and discontinuation in case of ejection fraction reduction of >20%. Symptomatic treatment, for example, with beta-blockers, can be given as advised by the cardiologist.

Arterial hypertension can be caused by BRAFi; for BRAFi+MEKi combinations, the MEKi also contributes to this side effect. The incidence for combination therapies with D+T, V+C and E+B were 29%, 16%, and 11%, respectively (table 2). Antihypertensive treatment should be pursued according to the existing guidelines.

Ocular events

Fluid accumulation (oedema) in the retina resulting in a serous neuroretinal detachment (SND) is a regular AE during treatment with BRAFi+MEKi (table 2). Although this AE is sometimes called serous retinopathy, chorioretinopathy, macular oedema or retinal pigment epithelial detachment, the term SND is preferable since the other terms refer to established diagnoses, with in part different clinical manifestations.[69] SND associated with BRAFi+MEKi is often asymptomatic, but may rarely cause transient visual disturbances, that is, blurred vision, reduced visual acuity, dyschromatopsia and photophobia.[70] The diagnosis is made with optical coherence tomography (OCT); the oedema is often bilateral and multifocal.[69 71]

After initiation of BRAF+MEK inhibition, SND occurs early within hours, days or weeks and is mostly caused by the MEKi.[69 71] Frequency of diagnosis depends on time and method of the ophthalmology examinations with an incidence of 13% or 8% of patients in the V+C and E+B trials, where regular OCT examinations were included (table 2). The pathogenetic mechanism is currently still unknown. SND is usually transient, but long-term experience is limited and retinal atrophy without functional relevance has been described.[72] Regular controls without any treatment are usually sufficient; however, in severe cases, dose interruption or reduction of the MEKi might be necessary.

Ocular inflammation (uveitis, conjunctivitis) is rarely induced by BRAFi. Here, topical steroids are usually sufficient for treatment; in severe cases, dose interruption or reduction of the BRAFi might be necessary.[73] In single cases, retinal vein occlusions have been described both during BRAFi and BRAFi+MEKi therapy.[73] In these cases, study protocols required discontinuation of BRAFi+MEKi and ophthalmological treatment. However, the frequency of retinal vein occlusions is similar in patients not treated with BRAFi+MEKi[74]; thus, the relation and the therapeutic consequences are unclear.

Taken together, ophthalmologic AEs (in particular SND) are frequent but often asymptomatic and transient; during treatment, ophthalmologic checks including OCT should be performed depending on visual disturbances.

Pulmonary events

Lung toxicity under BRAFi+MEKi therapy is infrequent. Cough, pneumonitis, sometimes accompanied by fever and pulmonary embolism may occur commonly.[75–77] Grade 3/4 events of interstitial lung disease or pneumonitis, subsumed rather under the term pneumonia in clinical studies, occurred in up to 2% of the cases (table 2). Pneumonitis is thought to be mainly caused by the MEKi.

In case of cough, shortness of breath or abnormal auscultation, chest CT should be performed. Lung infiltrates sometimes show a discrepancy to patient-reported symptoms. When an infectious origin has been ruled out via bronchoalveolar lavage, high dose of corticosteroids should be applied and tapered over time. While in severe cases, the MEKi has to be permanently discontinued, reinduction of the BRAFi after recovery is possible.

Renal events

Combined BRAFi+MEKi therapy can cause renal impairment, mostly as increase of serum creatinine. Acute renal failure or electrolyte disorders have been reported for all combination therapy[78 79] (table 2). A recent systematic review of BRAFi-mediated nephrotoxicity including pathology reports of kidney biopsies indicated tubule-interstitial damage with an acute and chronic component.[80–83]

In cases of higher grade acute kidney injury, BRAFi +MEKi therapy should be interrupted and reintroduced after improvement of renal function at a lower dose. As therapy with D+T frequently causes fever that may lead to dehydration of the patient—in cases of insufficient

Table 3 Recommendations for routine* monitoring of BRAF/MEK combination therapy

Test	Therapy start	Monthly control	Quarterly control
Blood count			
Differential blood count	x	x	
Clinical chemistry			
Electrolytes (Na, K, Ca, Mg)	x	x	
Creatinine	x	x	
CPK	x	x	
Troponin	x	(x)†	x
NT-proBNP	x	(x)†	x
Liver transaminases (AST, ALT, γ-GT)	x	x	
Bilirubin	x	x	
Examinations (non-laboratory tests)			
Skin inspection	x	x‡	x
Visual acuity control §	x	(x)¶	
Ocular OCT		(x)¶	
Blood pressure	x	x	
ECG	x	x‡	x
Echocardiography	x		(x)†

*In patients/situations without clinical particularities.
†In case of clinically abnormal signs (eg, heart, chest) or increasing CPK.
‡In months 1 and 2.
§Visual acuity (at therapy start) to be checked/noted (ie, in patient history).
¶in case of patient-reported visual disturbances.
γ-GT, gamma-glutamyl transferase;ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OCT, optical coherence tomography; x, test recommended; (x), test optional.

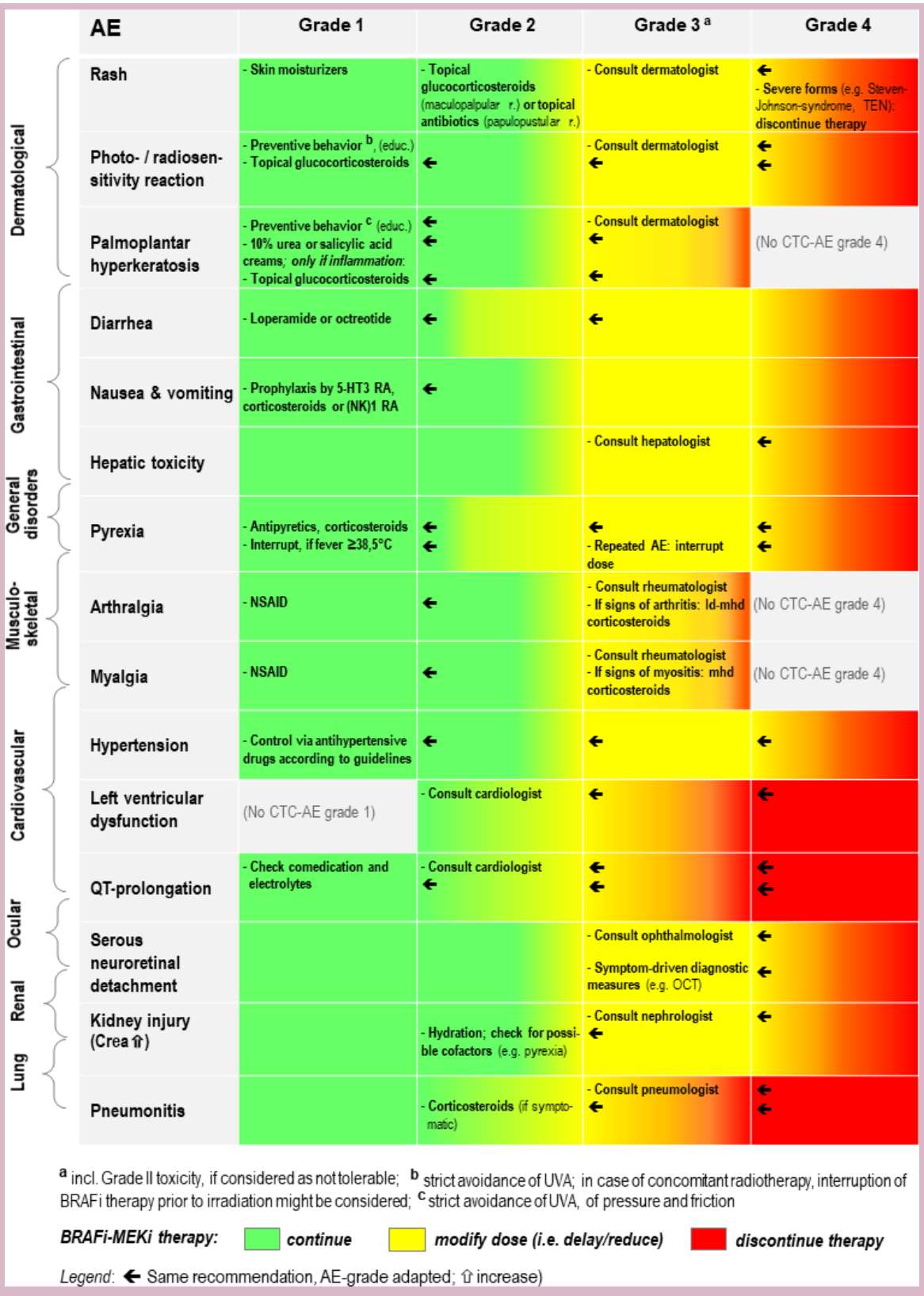


Figure 3 Recommendations for the management of clinically relevant and/or very frequent AE of BRAFi+MEKi therapy. Disclaimer: Official recommendations for the management of the three combinations might differ (please consider first the detailed specifications and recommendations as outlined in the summary of product characteristics (European Union) or in the respective, official prescribing information documents (USA and other countries outside European Union)). CTC-AE, common terminology criteria for adverse events; Crea, creatinine; ld, low-dose; mhd, middle-to-high-dose; NSAID, nonsteroidal anti-inflammatory drugs; OCT, optical coherence tomography; RA,receptor antagonist; TEN, toxic epidermal necrolysis; UVA, ultraviolet A (radiation).

oral fluid intake—pre-renal insufficiency may occur that ameliorates after rehydration of the patient.

DISCUSSION

BRAFi+MEKi combinations are highly effective in the therapy of metastatic melanoma[84 85] and D+T has additionally been shown to prolong overall survival in the adjuvant setting.[7] However, AEs occur in almost all (ie, ≥97%) of patients treated with D+T, V+C or E+B (table 1), with grade 3–4 AE rates of 46%–56%, 69% and 58%, respectively. Knowledge of side effect profiles, monitoring and management strategies are important to tailor the therapy to patients, diagnose side effects early, keep discontinuation rates low and guide patients through occurrences of such effects. This review is based on the available safety data from phase III clinical studies: our group's recommendations for the monitoring of side effects are provided in table 3, our recommendations for the management of clinically relevant and/or very frequent AEs of BRAFi +MEKi therapy are summarised in figure 3.

While some of the side effects are class effects, others are substance-specific. Differences in drug tolerability might partly be explained by their individual pharmacokinetic (figure 1) and pharmacodynamics characteristics.

Class-effects of BRAFi include gastrointestinal side effects, increases in transaminases and arthralgia as well as cutaneous toxicities with formation of secondary neoplasms.[20 22 23] For MEKi, class-effects encompass gastrointestinal side effects, increases in transaminases, oedema, ocular, cardiovascular AEs and cutaneous toxicity with the occurrence of papulopustular rash.[86–89] The frequency of papulopustular rash, described in MEKi monotherapy trials,[18 34 36] is decreased in combination regimens (figure 2). This is similar for the cutaneous side effects of BRAFi which are reduced by the suppression of the 'paradoxical activation' of the MAPK pathway, when adding a MEKi to the BRAFi. A systematic review indicates higher risk ratios for all grade diarrhoea, decreased ejection fraction and fever as well as a higher risk ratio for high grade diarrhoea when comparing BRAFi+MEKi versus BRAFi monotherapy.[90]

Substance specific, very common side effects include fever (for D+T) and photosensitivity (for V+C), attributed to the pharmacological properties of the BRAF inhibitors dabrafenib and vemurafenib. They were already identified during initial clinical development in BRAFi monotherapy trials.[12–15 20 22] Differences in side effect profiles can be used to adjust prescription to the individual patient, but also to switch between BRAFi+MEKi combinations when side effects occur.

Because frequencies of documented side effects also depend on the design of a given clinical study, its definition of monitoring intervals and its methods to assess safety parameters, comparisons across studies have limited validity. Since there are no head-to-head trials comparing D+T, V+C and E+B, the indirect comparison against vemurafenib is currently the best approximation (figure 2). The only published indirect treatment comparison, comparing BRAFi+MEKi combinations so far, concluded that D+T shows a more favourable toxicity profile than V+C.[24]

Like the published indirect treatment comparison between D+T and V+C, which itself provides a less strong evidence than a randomised head-to-head trial could do, our review has certain limitations. Since the confirmatory trials COMBI-V (D+T), CoBRIM (V+C) and COLUMBUS Part I (E+B) ended at different time points and had follow-up intervals of variable length (see online supplementary file 1), there is some analysis bias in favour of E+B, authorised for use in the USA and the European Union since July and September 2018, respectively, only. In addition, some publication bias must be considered, as case reports and case series, describing, for example, rare and very rare side effects as discussed in our review, have been issued so far mainly for D+T and V+C: late or additional cases reporting on a new BRAFi or a newly approved combination might maybe be less easily publishable too. By choosing—as the main source for the appraisal of AE and serious AE frequencies (tables 1 and 2)—three confirmatory trials comparing all against a common comparator, we attempted, however, to diminish analysis and publication bias.

In conclusion, BRAF plus MEK inhibitor therapy is an effective and safe therapy, if monitored adequately. Therefore, the treating physicians need to be familiar with side effect management to reduce morbidity and mortality as well as premature treatment discontinuation.

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