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REVIEW ARTICLE

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Why do we need a new BRAF-MEK inhibitor combination in melanoma?

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ABSTRACT

Despite the increasing role of immunotherapy, BRAF/MEK inhibitor combinations have still a central role in the treatment of *BRAF* V600-mutant melanoma. Encorafenib-binimetinib is the third BRAF-MEK inhibitor combination approved for the metastatic melanoma with *BRAF V600* mutation. Data from phase III trial demonstrated high antitumor efficacy and good tolerability of encorafenib-binimetinib. Compared to other combinations (dabrafenib-trametinib, vemurafenib-cobimetinib) the new combination showed favourable results in terms of the low rates of pyrexia and photosensitivity. Trials with triplet regimens that combine encorafenib-binimetinib with immunotherapy or a third targeted agent in an effort to overcome mechanisms of resistance to BRAF/MEK inhibition are ongoing.

Key words: advanced melanoma, *BRAF* mutation, encorafenib, binimetinib

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In the last few years, treatment of patients with *BRAF*-mutant advanced melanoma has changed radically, not only in terms of new therapeutic options, but also in terms of the number of available drugs. Molecularly targeted therapies (dabrafenib with trametinib, vemurafenib with cobimetinib) and immunotherapy (nivolumab, pembrolizumab, nivolumab with ipilimumab) have significantly improved overall survival in this group of patients [1–9]. Currently, a registered combination of BRAF/MEK inhibitors (encorafenib with binimetinib) is being added to this group.

Similarly to dabrafenib and vemurafenib, encorafenib is an ATP-competitive BRAF V600 kinase inhibitor. It differs from other drugs in this group by a more than 10 times longer dissociation half-life (> 30 h), which results in extended inhibition of mitogen-activated protein kinase (MAPK) signalling pathway [10]. It probably results in more potent anti-cancer activity, with a smaller paradoxical upregulation of MAPK pathway in healthy tissues responsible for the development of side effects [10, 11]. In turn, binimetinib is a selective inhibitor of MEK1 and MEK2 kinases, which are components of MAPK signalling pathway. Its effectiveness was also evaluated in patients with melanoma with a rare *NRAS* mutation (phase III NEMO study). However, the progression-free survival (PFS) improvement compared to dacarbazine (median 2.8 *vs.* 1.5 months) was too small to allow registration of a drug in this indication [12].

The activity of the combination of encorafenib with binimetinib in patients with metastatic *BRAF*-mutant melanoma was evaluated for the first time in a phase Ib/II study. The doses selected for phase II were 400, 450, or 600 mg daily for encorafenib and 90 mg daily for binimetinib. Response was observed in 72–78% of patients, and median PFS was 11.3 months [13]. These encouraging results led to a phase III trial (COLUMBUS) comparing the efficacy of encorafenib + binimetinib combination with vemurafenib and encorafenib in monotherapy. In the first part of this study, the patients were randomly assigned (1:1:1) to one of three arms, receiving: encorafenib at a dose of 300 mg/day,

Table 1. Summary of treatment outcomes according to COLUMBUS protocol

	COMBO450 n = 192		COMBO300 n = 258		ENCO300 (part 1+ 2) n = 280		WEMURAFENIB n = 191	
	Centrally assessed	Locally assessed	Centrally assessed	Locally assessed	Centrally assessed	Locally assessed	Centrally assessed	Locally assessed
Median PFS (months; 95% CI)	14.9 (11.0–18.5)	14.8 (10.4–18.4)	12.9 (10.1–14.0)	12.9 (10.9–14.8)	9.2 (7.4–11.0)	9.2 (7.4–11.1)	7.3 (5.6–8.2)	7.3 (5.7–8.5)
ORR (%; 95% CI)	63 (56–70)	75 (68–81)	66 (60–72)	73 (67–78)	50 (44–56)	56 (50–62)	40 (33–48)	49 (42–57)
CR (%)	8	16	8	11	5	8	6	7
PR (%)	55	59	58	62	45	49	35	42
Median DOR (mo.; 95% CI)	16,6 (12.2–20.4)	16.2 (11.1–20.4)	12.7 (9.3–15.1)	13.1 (10.8–16.6)	12.9 (8.9–15.5)	13.0 (9.5–15.0)	12.3 (6.9–16.9)	8.4 (5.8–11.0)

CI — confidence interval; CR — complete response; ORR — overall response rate; PR — partial response; DOR — duration of response

vemurafenib at a dose 1920 mg/day or, encorafenib at a dose of 450 mg/day in combination with binimetinib at a dose of 90 mg/day. In total 577 patients were enrolled with unresectable/metastatic *BRAF*-mutant melanoma without prior systemic treatment or after one prior immunotherapy line. At median follow-up of 16.6 months, independently assessed median PFS was 14.9 months in the encorafenib + binimetinib arm (95% confidence interval [CI]: 11.0–18.50), 7.3 months in the vemurafenib monotherapy arm (95% CI: 5.6–8.2), and 9.6 months (95% CI: 7.5–14.8) in the encorafenib monotherapy arm. Locally assessed median PFS values were similar. Hazard ratio (HR) was 0.54 for combination therapy *vs.* vemurafenib (p = 0.001) and 0.75 for combination therapy *vs*. encorafenib (p = 0.051) in independent assessment [14]. Of note, it is the first study showing a difference in efficacy of individual BRAF inhibitors in monotherapy (encorafenib *vs*. vemurafenib), which confirms the high specificity of BRAF kinase inhibition by encorafenib.

In October 2018 the overall survival (OS) data of patients treated in the first part of the COLUMBUS study were published [15]. Treatment with encorafenib at a dose of 450 mg/day in combination with binimetinib at a dose of 90 mg/day (COMBO450) reduced the risk of death compared to vemurafenib at a dose of 1920 mg/day (HR 0.61 [95% CI: 0.47–0.79], p < 0.001). Median OS was 33.6 months (95% CI: 24.4–39.2) for the patients treated with COMBO 450 *vs.* 16.9 months (95% CI: 14.0–24.5) for patients receiving vemurafenib. The three-year OS rate for the combination of encorafenib with binimetinib was 47%.

In the second part of the COLUMBUS study monotherapy with encorafenib at a dose of 300 mg/day was compared with a combination of encorafenib at a dose of 300 mg/day with binimetinib at a dose of 90 mg/day (COMBO300). Median PFS for combinations with encorafenib at a dose of 300 mg was 12.9 months (95% CI: 10.1–14.0) and was significantly longer compared to encorafenib monotherapy (HR 0.77, p = 0.029) but shorter compared to the combination COMBO450 [16]. This confirms the relationship between encorafenib dose and the effectiveness of combined therapy. Table 1 summarises the treatment outcomes in the COLUMBUS study, and Table 2 summarises the results of clinical trials with encorafenib and binimetinib.

The higher effectiveness of combination treatment is accompanied by better tolerance. Grade 3/4 adverse events (AEs) were observed less frequently in patients receiving encorafenib with binimetinib (combination therapy — 58%, vemurafenib — 63%, encorafenib — 66%), similarly to AEs requiring treatment interruptions or dose modification. The maximum dose of encorafenib used as monotherapy, determined based on previous research, is 300 mg/day [10]. The addition of binimetinib improved tolerance of encorafenib to the extent that the dose of encorafenib used in the combination was increased to 450 mg/day, which contributed to higher treatment effectiveness. However, it should be remembered when modifying treatment to reduce the dose of encorafenib to 300 mg/day in case of an interruption or withdrawal of binimetinib.

The most common AEs observed in patients receiving combination therapy are gastrointestinal tract disorders (app. 30–40%), increased creatine kinase activity (23%), and fatigue (29%). Whilst gastrointestinal tract disorders occurred more often than in patients receiving monotherapy, muscle and joint pains, skin complications (such as rash, hyperkeratosis, hand-foot syndrome, and hypersensitivity to light), as well as hair loss were less frequent. AEs specifically related to MEK inhibition, such as exudative serous chorioretinopathy (20–23%) and left ventricle functional disorders (2%), occurred more frequently during combination treatment [14, 15].

The nature of AEs is similar in all BRAF/MEK inhibitor combinations; only their prevalence is different. Fever, which is a typical AE of dabrafenib with

Table 2. Summary of clinical trials of encorafenib and binimetinib

Study (year)	Study design	Efficacy outcomes	Safety outcomes
Ascierto et al. (2013) [9]	Multicentre, open phase II study, BINI 45 mg twice daily in melanoma patients with *NRAS* (n = 30) and *BRAF* (n = 41) mutation	Investigator-assessed RR: 20% in patients with *NRAS* and *BRAF* mutations (6/30 and 8/41 patients) PR confirmed in only 3 and 2 patients, with no CR SD in 13 (42%) NRAS+ patients and 13 (32%) *BRAF*+ patients Survival: — median PFS for *NRAS*+: 3.7 months (95% CI: 2.5–5.4) — median PFS for *BRAF*+: 3.6 months (95% CI: 2.0–3.8)	Common AE (*NRAS*+ and *BRAF*+; n = 71): acne-like dermatitis (46%), peripheral oedema (34%), diarrhoea (32%), elevated CPK activity (28%), ocular toxicity (18%) Grade 3/4: 4 (5.6%) patients Treatment discontinuation due to AE: 15 (21%) patients Dose reduction due to AE: 33 (46%) patients
Dummer et al. (2017) NEMO [12]	Multicentre, open phase III study, randomisation 2:1: BINI 45 mg twice daily (n = 269) *vs*. DTIC 1000 mg/m^2 IV every 3 weeks (n = 133) in melanoma patients with *NRAS* mutations	Confirmed RR: 15.2% for BINI (95% CI: 11.2–20.1) *vs*. 6.8% for DTIC (95% CI: 3,1–12,5); p = 0.015 SD: 40.5% (BINI) *vs*. 17.3% (DTIC) Survival: — median PFS: 2.8 months (95% CI: 2.8–3.6) for BINI *vs*. 1.5 months (95% CI: 1.5–1.7) for DTIC (HR: 0.62; p < 0.001)	Common AE (BINI): increased CPK activity (42%), diarrhoea (40%), peripheral oedema (36%), rash (36%), acne-like dermatitis (35%), ocular toxicity (17%) Severe AE: 91 (33.8%) patients, treatment discontinuation due to AE: 66 (24.5%) patients Dose reduction due to AE: 163 (60.6%) patients
Dummer et al. (2018) COLUMBUS [14]	Multicentre, open phase III study, randomisation 1:1:1 (n = 577): ENCO 450 mg once daily + BINI 45 mg twice daily (COMBO) *vs.* VEM 960 mg twice daily *vs*. ENCO 300 mg once daily (part 1) in melanoma patients with *BRAF* mutations	COMBO *vs*. VEM *vs.* ENCO Confirmed RR: 63% (56–70) *vs*. 40% (33–48) *vs*. 51% (43–58) Survival: — median PFS: 14.9 months (11.0–18.5) *vs*. 7.3 months (5.6–8.2) *vs*. 9.6 months (7.5–14.8); HR: 0.54 for COMBO *vs.* VEM (p = 0.001) and 0.75 for COMBO *vs*. ENCO (p = 0.051) — median OS for COMBO: 33.6 months	Common AE (COMBO only): nausea (41%), diarrhoea (36%), vomiting (30%), fatigue (29%), arthralgia (26%), elevated CPK activity (23%), headache (22%), fever (18%), ocular toxicity (13%) Grade 3/4 AE: 58% of patients Treatment discontinuation due to AE: 16 (8%) patients Dose reduction due to AE: 21 (11%) patients Dose interruption due to AE: 88 (46%) patients

BINI — binimetinib; RR — response rate; PR — partial response; CR — complete response; SD — stable disease; PFS — progression-free survival; AE — adverse event; CPK — creatine phosphokinase; DTIC — dacarbazine; IV — intravenously; HR — hazard ratio; ENCO — encorafenib; VEM — vemurafenib

trametinib (> 50% of patients), occurs less frequently in patients receiving combinations of encorafenib with binimetinib (18%) and is not recurrent. Phototoxicity, also called photoirritation, which in turn occurs in half of the patients treated with vemurafenib with cobimetinib, affects only 5% of patients treated with encorafenib and binimetinib. Table 3 presents detailed data regarding therapy tolerance in the COLUMBUS study.

The results of the COLUMBUS study led to the registration of a combination of encorafenib with binimetinib by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of patients with unresectable/metastatic melanoma with *BRAF* mutation.

As combinations of BRAF/MEK inhibitors have been used in daily clinical practice for several years, attempts to modify the treatment in order to extend the response duration or breaking the resistance to molecularly targeted drugs has become more interesting. There are a few clinical trials ongoing at the present time: IMMU-TARGET (NCT02902042), assessing the effectiveness of combination of encorafenib and binimetinib with anti-PD1 antibody, pembrolizumab; SECOMBIT (NCT02631447), assessing the optimal treatment sequence — encorafenib + binimetinib in the first line, nivolumab + ipilimumab in the second line — in comparison with the reverse sequence; EBIN (NCT03235245), assessing the effectiveness of immunotherapy (nivolumab + ipilimumab) preceded by a 12-week induction phase with the use of encorafenib and binimetinib; and LOGIC2, in which patients after failure of treatment with encorafenib and binimetinib receive further combinations of drugs based on the assessment of molecular disorders in cancer tissue collected after disease progression. Activity of encorafenib and binimetinib is also evaluated in patients with metastatic colorectal cancer with *BRAF* mutation (phase III BEACON CRC study, NCT02928224).

Table 3. The most frequent adverse events in the arms containing encorafenib in the phase III COLUMBUS study

	COMBO300 n = 257		ENCO300 (part 1 + 2) n = 276		COMBO 450 n = 192	
Median duration of treatment exposure (weeks)	**52.1**		**31.5**		**51**	
Adverse events (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Diarrhoea	28	2	12	1	36	3
Nausea	27	2	36	3	41	2
Joint pain	22	1	43	8	26	1
Fatigue	22	1	26	1	29	2
Elevated creatine kinase activity	20	5	1	0	23	7
Vomiting	15	< 1	25	4	30	2
Elevated GGTP activity	14	5	11	4	15	9
Muscle pain	14	< 1	27	8	14	0
Alopecia	13	0	49	< 1	14	0
Headaches	12	< 1	26	3	22	2
Elevated ALT activity	11	5	4	1	13	6
Skin hyperkeratosis	10	0	39	3	14	1
Dry skin	8	0	28	0	14	0
Rash	15	1	43	5	23	1
Palmoplantar keratoderma	7	< 1	24	1	9	0
Palmar-plantar erythrodysesthesia syndrome	4	< 1	47	11	7	0
Fever	17	0	16	0	18	4
Left ventricle malfunctions	6	1	3	1	8	2

GGTP — gamma-glutamyl transpeptidase; ALT — alanine aminotransferase

Table 4. Phase III studies with BRAF or MEK inhibitors alone or in combination in the treatment of advanced melanoma

Authors	**Long et al. 2014 [8] Long et al. 2017 [1]**		**Robert et al. 2015 [5]**		**Larkin et al. 2014 [9] Ascierto et al. 2016 [6]**		**Dummer et al. 2018 [14, 15]**	
Drug	**Dabrafenib**	**Dabrafenib + trametinib**	**Vemura-fenib**	**Dabrafenib + trametinib**	**Vemura-fenib**	**Vemurafenib + cobimetinib**	**Encorafenib + binimetinib COMBO 450**	**Encorafenib + binimetinib COMBO 300**
ORR (%)	53	69	51	64	50	70	63	66
Median PFS (months)	8.8	11	7.3	12.6	7.2	12.3	14.9	12.9
Median OS (months)	18.7	25.1	18.0	25.6	17	22.3	33.6	
2-/3-year OS rate	43/32%	52/44%	39/31%	53/45%			2-year OS rate: 57.6%	

ORR — overall response rate; PFS — progression-free survival; OS — overall survival

Conclusions

Encorafenib with binimetinib is already the third registered combination of BRAF/MEK inhibitors. Results of a phase III study showed very good tolerance of this treatment and the best survival among all available combinations of targeted therapies in terms of both PFS and OS. Table 4 summarises the results of clinical trials with various BRAF/MEK inhibitors. Undoubtedly, it is difficult to directly compare the survival of participants in these clinical studies, so a randomised clinical trial is needed. The better results of treatment with

encorafenib and binimetinib can be explained by slightly different patient populations (e.g. a lower percentage of patients with elevated lactate dehydrogenase activity) or better access to immunotherapy in subsequent treatment lines. On the other hand, median PFS and OS in patients treated with vemurafenib in the COLUMBUS study are very close to those observed in the coBRIM or COMBI-v studies. Higher efficacy of therapy can therefore result simply from better pharmacological properties of encorafenib. In conclusion, a combination of encorafenib with binimetinib is a valuable distinctive alternative to other drug combinations.

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