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Drug Evaluation: The combination of vemurafenib and cobimetinib in advanced melanoma

*Lavinia Spain, Emily Goode, Yevette McGovern, Kroopa Joshi, James Larkin**

Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ,

United Kingdom (all authors)

**corresponding author:* james.larkin@rmh.nhs.uk; ph: +44 20 7352 8171

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Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ, United Kingdom (all authors)

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Abstract

Introduction: Advanced melanoma with a *BRAF V600* mutation responds to treatment with BRAF inhibitors such as vemurafenib, with great improvement in tumour response and patient survival. Despite early and often dramatic responses, resistance to vemurafenib develops. Concurrent inhibition of a downstream protein, MEK, also involved in the MAPK oncogenic signalling pathway, defers development of resistance. The MEK inhibitor cobimetinib has been successfully and safely combined with vemurafenib, further improving response rate and survival when compared to vemurafenib monotherapy.

Areas covered: This article covers the mechanism of action of both vemurafenib and cobimetinib, in addition to describing results from the key Phase I and Phase III studies which led to registration of the combination in the US and Europe as a therapeutic option for advanced *BRAF* mutant melanoma. The safety profile of these agents is also discussed in detail, including similarities with and differences from the competitor compounds dabrafenib and trametinib.

Expert opinion: Vemurafenib in combination with cobimetinib provides an

alternative BRAF/MEK blockade. The combination is tolerable, safe and effective and results in fewer skin toxicities than vemurafenib monotherapy.

Keywords

Vemurafenib, cobimetinib, advanced melanoma, *BRAF* mutation, MAPK pathway

1.1 Introduction

Malignant melanoma is the most aggressive form of cutaneous malignancy with approximately 132,000 new cases diagnosed globally each year. In the UK, it is the 5th commonest cancer accounting for nearly 13,000 cases and over 2000 deaths a year.[1] The incidence of melanoma is rising steadily with a doubling of the number of cases every decade, a rate of increase more rapid than any other form of solid cancer. Historically, advanced cutaneous melanoma has been associated with an extremely poor outlook; until recently the median survival of such patients was in the order of 6 to 9 months, with only 10-15% of patients alive at 3 years.[2]

Approximately 50% of cutaneous melanomas harbour a *BRAF V600* mutation resulting in constitutive BRAF activation, integral to oncogenic signalling via the mitogen activated protein kinase (MAPK) pathway.[3, 4] This discovery has led to the development of several molecular targeted therapies in recent years. The BRAF inhibitors vemurafenib and dabrafenib demonstrated a significant improvement in progression-free and overall survival as compared with standard chemotherapy alone in patients with advanced *BRAF V600E* mutated melanoma, leading to their approval.[5, 6]

Despite the impressive initial responses demonstrated with BRAF inhibition in advanced melanoma, these are short-lived for the vast majority of patients with most developing resistance to therapy within 6 to 9 months.[5, 6] Multiple mechanisms of acquired resistance are described; amongst these reactivation of the MAPK signalling pathway accounts for acquired resistance in the large majority of patients.[7] MEK is a protein downstream of BRAF and one such mode of MAPK reactivation. Accordingly, large-scale clinical trials have demonstrated combination BRAF/MEK inhibitor therapy to have superior clinical efficacy than BRAF inhibition alone with an improvement in progression-free survival and overall survival in patients with BRAF-mutated melanoma.[8-10] This article focuses on the combination of vemurafenib with cobimetinib.

1.2 Overview of the market

In a renewed era of cancer immunotherapy, the FDA approval of novel immunomodulatory antibodies targeting T cell immune checkpoint molecules has led to a change in the management of *BRAF*-mutated melanoma with anti-CTLA-4 and anti-PD-1 therapy incorporated into various clinical guidelines. The recommendation from the European Society for Medical Oncology (ESMO) for the treatment of *BRAF*-mutated melanoma comprises first-line anti-PD-1 treatment or combined BRAF/MEK inhibitor therapy.[11] In the United States, National Comprehensive Cancer Network (NCCN) guidelines recommend using any of the following regimens in the first-line setting for patients with *BRAF*-mutated melanoma: combined BRAF/MEK inhibition, single agent BRAF

inhibition, single agent anti-PD-1 therapy or combined anti-PD-1 and anti-CTLA-4 therapy.

In addition to clinical concerns regarding drug resistance, toxicity and tolerability of currently available molecular targeted drugs and immune checkpoint antibodies, well-defined treatment algorithms regarding the optimal sequence and timing of immunotherapy and molecular targeted therapy in *BRAF*-mutated melanoma remain a significant unmet clinical need in the management of metastatic melanoma.[12] In patients with *BRAF*-mutated melanoma, in the context of symptomatic, large volume, rapidly progressive disease most clinicians favour use of targeted molecular therapy in the first instance where the priority is to achieve a rapid response. On the contrary, checkpoint blockade may be adopted first-line in patients with more indolent disease, reserving molecular targeted agents as salvage therapy at the time of disease progression.

Two different BRAF/MEK inhibitor combinations are currently in use: dabrafenib/trametinib and vemurafenib/cobimetinib. Encorafenib plus Binimetinib is currently being tested in a phase III trial and data is awaited (NCT01909453). Several second-generation immune checkpoint modulators are being tested in clinical trials including anti-LAG-3, anti-4-1BB and anti-GITR therapies reflecting the significant interest in cancer immunotherapy following the recent clinical successes of various anti-PD-1 therapies.[13]

2.1 Introduction to the compounds

Vemurafenib and cobimetinib inhibit BRAF and MEK proteins, respectively, within the MAPK pathway. This is the key growth signalling pathway in *BRAF V600*-mutated melanoma cells and is represented in Figure 1.

Vemurafenib is an oral tyrosine kinase inhibitor administered twice a day at a dose of 960mg (each tablet contains 240mg), continuously. Cobimetinib is an oral tyrosine kinase inhibitor targeting the MEK protein. It is administered at a dose of 60mg (each tablet contains 20mg) daily, for three weeks out of four.

Melanoma cells eventually develop resistance to BRAF inhibitor monotherapy via one of several mechanisms, for example by reactivation of the MAPK pathway through MEK signalling[7, 14], CRAF upregulation[15] and development of NRAS mutations[16, 17], amongst others. Combined blockade of BRAF and MEK proteins defers development of resistance, allowing prolonged MAPK inhibition and therefore more durable tumour control. Concurrent blockade not only defers resistance, it also alters the side effect profile of both agents.

2.2 Chemistry

Vemurafenib has the chemical name propane-1-sulfonic acid [3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4- difluoro-phenyl]-amide and the molecular formula C23H18ClF2N3O3S.[18]

Cobimetinib fumarate has the chemical name chemical name (*S*)-[3,4-difluoro-2-(2-fluoro-4-292 iodophenylamino)phenyl] [3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate and the molecular formula

$C_{46}H_{46}F_6I_2N_6O_8$ ($2\ C_{21}H_{21}F_3IN_3O_2 \cdot C_4H_4O_4$).[19]

2.3 Pharmacodynamics

Vemurafenib targets the mutant BRAF protein, inhibiting downstream protein phosphorylation of MEK. Ultimately this induces cell cycle arrest and apoptosis and thereby inhibits cellular proliferation and unregulated tumour growth. Vemurafenib was specifically engineered to provide greater inhibition of the mutant BRAF protein over the wild-type BRAF protein.[20, 21] This enables higher drug concentration exposure, without serious side effects imposed upon *BRAF* wild-type tissues.[22]

Cobimetinib binds to active, phosphorylated MEK 1/2 proteins in a selective manner.[23] In doing so it prevents downstream phosphorylation of ERK and resultant oncogenic signalling. The dependency of *BRAF* mutated tumours on MEK signalling makes this a particularly rational combination.[24]

Inhibition of MEK concurrent with BRAF results in less hyperkeratotic skin toxicity, including reduced development of squamous cell carcinomas. This toxicity is due to a paradoxical increase in MAPK signalling induced by BRAF inhibition, with secondary lesions often demonstrating a mutation in *RAS*, especially *HRAS*.[25] Mutant *RAS*-driven increased signalling may also precipitate the development of RAS-mutant tumours, such as colorectal and pancreatic cancer.[26, 27] It is possible that MEK inhibition can mitigate but not completely abrogate this process.[26]

2.4 Pharmacokinetics and metabolism

The pharmacokinetics of vemurafenib and cobimetinib are summarised in Table 1. Vemurafenib is a moderate CYP1A2 inhibitor and can also induce CYP3A4, its main metabolic pathway. Prescribers need to be aware of potential increased side effects and decreased efficacy of concurrent medications metabolised by these pathways. Concurrent use of medications with strong CYP3A4 inhibitory properties should be avoided in conjunction with cobimetinib, or if essential, close monitoring for adverse events should be instituted.

3.0 Clinical efficacy

3.1 Phase I trial

A phase 1b study in advanced *BRAF* mutated melanoma assessed the safety of combination vemurafenib/cobimetinib with dose escalation in patients that were either naïve to BRAF inhibition (n=63) or had previously progressed on vemurafenib (n=66).[28] Efficacy of combination therapy was measured as a secondary end point. Ten dosing regimens were chosen and 2 were escalated: vemurafenib 720mg BD with cobimetinib 60mg, 21 days on ad 7 days off, and vemurafenib 960mg BD with cobimetininb 60mg BD, 21 days on and 7 days off. The overall response rate (ORR) was 15% in patients who had previously received vemurafenib and 87% in BRAF inhibitor naïve patients, with a complete response (CR) rate of 10% and median progression free survival (PFS) of 13.7 months (95% CI 10.1-17.5) in this latter group. This was notably longer than the median PFS with vemurafenib monotherapy, reported at less than 7 months

(95% CI 2.6-3.4).[29, 30] After extended follow up, the median OS in BRAF inhibitor naïve patients was reported as 31.2 months, with an OS of 37% at 3 years.[31]

3.2 Phase III trial

Larkin et al demonstrated the superior clinical efficacy of vemurafenib/cobimetinib in the Phase 3 coBRIM study in 2014.[32] Four hundred and ninety five patients with unresectable locally advanced or metastatic *BRAF V600* mutated melanoma were assigned to receive either vemurafenib/cobimetinib (combination) or vemurafenib/placebo (control) in the first line setting. The combination group had a significantly improved median PFS of 9.9months compared to 6.2 months, with HR of 0.51 for death or disease progression (95% CI 0.39-0.68, p<0.001). The rate of partial response (PR) or CR was 68% compared to 45% in the control group. Consistent with the phase 1 results, there was a non-significant increase in grade 3 or 4 adverse events in the combination group, including elevated creatine kinase and liver function tests, with no increased rate of discontinuation of treatment. Furthermore, there was a decreased incidence of squamous cell carcinoma (SCC) incidence in the combination group.

Updated coBRIM results at 14.2 months' follow-up confirmed the clinical benefit of combination treatment.[33] The median PFS was 12.3 months in the combination group, compared to 7.2 months in the control group, HR 0.58 (95% CI 0.46-0.72). The ORR was 70% in the combination group versus 50%, with CR in 16% vs 11% in the control group. At 18.5 months follow up the median OS was 23.3 months in the combination group versus 17.4 months (HR, 0.70; 95%

CI, 0.55-0.90; *P* = .005), and 2 year OS 48% versus 38%.[34] Clinical benefit was seen consistently across mutation types, including *BRAF V600E* and *V600K* and presence of *RAS* or *RTK* mutations did not affect clinical outcomes.[35]

In addition, health related quality of life was assessed with the EORTC QLQ-C30 questionnaire and reported better scores in all functioning domains of the questionnaire in the combination group after baseline, but not all reached clinically meaningful (CM) criteria.[36] The CM criteria were met for improvements in insomnia, fatigue, social functioning and pain but as predicted the combination group had worsening of diarrhoea.

Post-marketing surveillance is yet to be reported for this combination, although a large safety study on vemurafenib monotherapy did not raise any new safety signals.[37]

Table 2 summarises the efficacy results from the Phase I and III trials of vemurafenib/cobimetinib and dabrafenib/trametinib.

3.3 Ongoing trials

There are a number of other ongoing studies assessing BRAF and MEK inhibition with combination vemurafenib and cobimetinib, including a second Phase 3 study (NCT02427893) comparing this combination with 10 days of monotherapy of either drug prior to combination treatment.

The optimisation of dosing and sequencing is also being explored in a phase 2 study comparing intermittent and continuous dosing (NCT 02583516). Intermittent vemurafenib was shown to increase drug tolerability without obviously limiting efficacy in a small case series.[38] Therefore, intermittent dosing of vemurafenib in combination treatment may provide a similar benefit. Intermittent combination treatment was given safely to a patient with *BRAF* mutant melanoma who developed rapid progression of *NRAS*-mutant leukaemia on vemurafenib. He received a further 35 weeks of combination treatment with vemurafenib and cobimetinib. Response has been maintained at nearly twenty months, illustrating that there is potential for such an approach.[39]

There is also an ongoing trial (NCT02537600 CONVERCE) to determine the intracranial efficacy of this combination in *BRAF* mutated metastatic melanoma patients with brain metastases. Another similar phase 2 study was unfortunately terminated early due to slow accrual (NCT02230306 coBRIM-B).

Surgery continues to play an important role in Stage I to III melanoma as well as in selected cases of Stage IV disease. The potential role of combination targeted therapy in the treatment paradigm requires consideration, for example to optimize the surgical approach or convert from unresectable to resectable disease. Combination vemurafenib and cobimetinib is being assessed in the neoadjuvant setting with patients who have palpable lymph nodes (stage IIIB/IIIC) receiving 2 months of treatment prior to surgery and adjuvant combination treatment to a maximum of 12 months (NCT02036086). Another Phase 2 study is also assessing neoadjuvant combination therapy over 18 weeks

in stage IIIC/IV disease and also aims to identify predictive and prognostic biomarkers (NCT02303951). A phase III trial of dabrafenib and trametinib following surgery for patients with high risk *BRAF V600* mutation positive melanoma (COMBI-AD) is ongoing and results are awaited (NCT01682083). Similarly, a phase III study of vemurafenib monotherapy given to patients with *BRAF V600* mutant melanoma in the adjuvant setting has closed to accrual and outcomes are pending (NCT01667419).

Whilst the combination of vemurafenib and cobimetinib has shown promising results, further research into maximising response rates and efficacy by adding other targeted treatments is important. The phase 2 study examining the benefit of additional bevacizumab was terminated due to toxicity and slow accrual (NCT01495988). However, there are active studies to assess the safety and efficacy of future combinations, including the addition of decitabine, which disrupts DNA methylation (NCT01876641) and may give benefit to BRAF inhibitor resistant melanoma patients.

Finally, with the success of immunotherapy in melanoma treatment in the last decade it is important to investigate the impact of targeted therapies on the tumour immune microenvironment.

A Phase 2 study (NCT01813214) will explore the effect of vemurafenib and cobimetinib on the immune response to melanoma, including T cell infiltration and the presence and expression of immune mediating proteins and genes.

There is also a Phase 1b study (NCT01656642) comparing vemurafenib alone or in combination with cobimetinib with the addition of an anti-PD-L1 drug (atezolizumab) in both cohorts in *BRAF* mutant metastatic melanoma.

4. Safety and tolerability

Trials of vemurafenib have established the common adverse events observed with this drug when used as monotherapy. These include rash (42%), fatigue (45%), arthralgia (58%), photosensitivity (41%), cutaneous squamous cell carcinoma (19%), nausea (40%) and raised liver function tests (36%).[40]

Data regarding cobimetinib as a monotherapy in advanced melanoma is not published, however the MEK inhibitor trametinib was studied in a Phase III trial by Flaherty et al and the most common adverse events noted included rash (57%), diarrhoea (43%), fatigue (26%) and peripheral oedema (26%). Other notable events included reduced ejection fraction/left ventricular dysfunction (7%) and one case of chorioretinopthy.[41] These appear to be class-effects with MEK inhibitors.

In terms of the combination of vemurafenib with cobimetinib, a Phase Ib study by Ribas et al of vemurafenib/cobimetinib saw 129 patients treated with ten different dosing regimens of the combination, in pursuit of the maximum tolerated dose (MTD).[28] This was established as vemurafenib 960mg twice daily continuously and cobimetinib 60mg daily for 3 out of every 4 weeks – ie using the maximal single-agent tolerated doses. The study included two populations: 66 patients who had recently progressed on vemurafenib and 63 who were naïve

to both compounds. In all dosing regimens the most common adverse events were diarrhoea (64%), non-acneiform rash (60%), liver enzyme abnormalities (50%), fatigue (48%), nausea (45%), and photosensitivity (40%). Most events were of mild-moderate severity. The most common grade 3 or grade 4 events included cutaneous squamous cell carcinoma (9%), raised alkaline phosphatase (9%) and anaemia (7%). The combination naïve group had more adverse events than those previously treated with vemurafenib, likely reflecting a reporting bias.

In the Phase III coBRIM trial of vemurafenib/cobimetinib compared with vemurafenib/placebo, the overall rates of adverse events were similar in both arms for all grades of toxicity.[32] The most common adverse events seen with combination treatment were diarrhoea (56%), nausea (40%), rash (39%), arthralgia (32%), fatigue (32%), fever (26%), elevated ALT and AST (24 and 22% respectively) and vomiting (21%). The patients receiving vemurafenib alone had fewer events of diarrhoea (28% vs 56%), nausea (24% vs 40%) and vomiting (13% vs 21%), but a higher rate of cutaneous squamous cell carcinoma (11% vs 3%), hyperkeratosis (29% vs 10%) and arthralgia (40% vs 32%). Grade 3 adverse events occurred in 49% in both arms. The majority of Grade 3 events seen in the combination arm were abnormal blood results with raised creatine kinase (CK; 7%), raised ALT (11%) and AST (8%), as well as diarrhoea (6%), rash (5%), and fatigue (4%). In the vemurafenib monotherapy group the most common grade 3 events were cutaneous SCCs (11%), raised ALT (6%), rash (5%) and arthralgia (5%). Eight percent of subjects suffered a reduced ejection fraction, Grade 3 in 1%, and 4% developed a prolonged QT interval, Grade 3 in

1%. The incidence of toxic events requiring drug withdrawal was similar in both groups (12% in the monotherapy and 13% in the combination group).

The rate of serous retinopathy is greater with vemurafenib/cobimetinib than vemurafenib alone, with 26% versus 3% of patients impacted in the coBRIM trial.[42] The majority of events were grade 1 or 2 (88%) and mostly picked up on routine surveillance. In the few cases where drug therapy was interrupted or reduced, 75% resolved or were resolving at the time of reporting. Median time to onset was early in treatment at 1 month.

In the coBRIM trial, 9 patients died from treatment-related causes: 3 in the vemurafenib arm (1%) and 6 (2%) in the combination arm. With such small numbers, one cannot determine whether this difference is significant. The causes of death ranged from general disorders including fatigue to cardiac events. Two neurological events occurred in the combination group: cerebral haemorrhage and hemiparesis.[32]

In a Phase III trial of the alternative BRAF and MEK inhibitors dabrafenib and trametinib in combination compared with dabrafenib alone, the overall adverse event rates were very similar. Notable differences included higher rates of fever with the combination (52% vs 25%) but fewer episodes of hyperkeratosis (6% vs 33%), cutaneous squamous cell carcinoma (3% vs 9%) and alopecia (5% vs 26%) than seen in the dabrafenib monotherapy arm.[9] Comparing across studies of vemurafenib/cobimetinib and dabrafenib/trametinib, fever is seen more commonly with dabrafenib/trametinib (52% vs 26%), whereas diarrhoea (56%

vs 18%), rash (39% vs 24%), nausea (40% vs 20%) arthralgia (32% vs 16%) and hyperkeratosis (10% vs 6%) are more common with the combination of vemurafenib/cobimetinib. Hyperkeratosis and squamous cell carcinomas occurred much less commonly in the combination BRAF/MEK inhibitor groups of both Phase III trials relative to BRAF inhibitor monotherapy.[8, 32]

Table 3 outlines adverse events of vemurafenib and cobimetinib compared with vemurafenib monotherapy and the combination of its competitor dabrafenib and trametinib.

5. Regulatory affairs

Vemurafenib is licensed in the United States (US), Europe and Australia for use as monotherapy. Cobimetinib is also now licensed for use in combination with vemurafenib in the United States (for *BRAF V600E* and *V600K* mutations) and in Europe (for *BRAF V600* mutations) for advanced melanoma, but is not yet licensed in Australia.

6.1 Conclusion

The combination of vemurafenib with cobimetinib is a highly effective treatment option for patients with advanced BRAF mutant melanoma. The addition of cobimetinib results in improved response rates as well as significantly longer progression-free and overall survival. Availability of this combination provides an alternative to the combination of dabrafenib with trametinib, with the schedule and toxicity profile differing between the two combinations. The Drug Summary Box provides an overview of this combination.

6.2 Expert opinion

The combination of vemurafenib with cobimetinib provides an alternative to dabrafenib and trametinib in patients with advanced *BRAF* mutant melanoma. Our practice is to reserve these combinations for use in patients with a critical burden of disease, or brain-predominant disease, given their high objective response rates (around 70%)[8, 32] and the efficacy of BRAF monotherapy in the treatment of central nervous system lesions[43, 44], from which we extrapolate that the combination will be at least as effective. Use of vemurafenib/cobimetinib upfront, as opposed to addition of cobimetinib later, is the most appropriate way to initiate this therapeutic combination.

Though similar in efficacy, the adverse event profile of vemurafenib/cobimetinib differs from dabrafenib/trametinib in a number of areas. Febrile episodes are less common. On the other hand, its more complex, intermittent dosing schedule and greater number of tablets (due to relatively less bioavailability than dabrafenib/trametinib) may make it less preferable to some. The photosensitivity associated mainly with vemurafenib can be problematic for anyone regularly exposed to sunlight and the higher rates of diarrhoea, rash, nausea and arthralgias may have a significant impact on quality of life. The availability of this combination is unlikely to change current drug-treatment strategies, however marketplace competition may increase availability of BRAF/MEK combination therapies as less exclusivity could reduce the price. The outcome of the Phase III trial with encorafenib and binimetinib (NCT01909453) may see a third combination become available.

Physicians should feel comfortable in prescribing this combination, but need to counsel patients appropriately regarding expected side effects. Out practice is to recommend high SPF-factor sunscreen and avoidance of direct sunlight to prevent photosensitivity, as well as to prescribe prophylactic anti-emetics and anti-diarrhoeal medication. Although the addition of cobimetinib to vemurafenib elevates risk of cardiac dysfunction and ocular toxicity, we do not routinely undertake echocardiograms and ophthalmology review. High risk patients, or those who develop symptoms suggestive of one of these rare side effects, should have a prompt clinical assessment. There is also potential for radiation recall and sensitization when vemurafenib and radiotherapy are combined. The skin is particularly vulnerable but other organs may be impacted. In November 2015 the UK government issued a specific warning to this effect.[45]

The careful development of vemurafenib provides an example of how an active agent may be potentiated to allow greater specificity for a target, resulting in both superior clinical efficacy and tolerability.[21] The ORR of 80% in the Phase I trial is testament to this.[28] The concept of dual MAPK protein blockade to defer resistance may be further exploited as technology enables us to design effective RAS and ERK inhibitors. Patients may change their co-inhibitor at -or ideally just prior to- clinical progression, based on the mechanism of developed resistance. In terms of alternative scheduling, there is preclinical evidence supporting evaluation of an intermittent dosing approach. Research in mice has shown that vemurafenib-resistant melanomas become drug-dependent for their proliferation and may regress upon drug cessation.[46]

Although the original study looking at combination vemurafenib with ipilimumab, an anti-CTLA4 antibody, resulted in significant hepatotoxicity[47], the potential for synergy remains and ongoing trials are in progress, as discussed above. Our understanding of the way in which BRAF inhibition and therapeutic resistance may alter the tumour microenvironment is expanding.[48] Trials such as SECOMBIT (NCT02631447) will enable further insight into the best way of sequencing BRAF/MEK inhibition with immune checkpoint blockade.

Finally, use of vemurafenib/cobimetinib may not be limited to use in advanced melanoma patients in future. As already discussed in the Clinical Efficacy section, use in the neoadjuvant setting may improve both surgical and disease outcomes and we await results from ongoing trials to elucidate this.

Drug summary box

Drug names (generic)	Vemurafenib and cobimetinib
Phase	Licensed in the US and Europe
Indication (specific to discussion)	Advanced melanoma with a *BRAF V600* mutation (ie unresectable Stage III or Stage IV disease).
Pharmacology and mechanism of action	Both agents are tyrosine kinase inhibitors targeting MAPK pathway proteins. Vemurafenib selectively inhibits the mutant BRAF protein where cobimetinib binds to MEK in its activated, phosphorylated form. This results in reduced oncogenic signally, tumour cell cycle arrest and apoptosis and translates into improved clinical outcomes.
Route of administration	Both are administered orally in tablet form.
Pivotal trial	combination vemurafenib/cobimetinib over vemurafenib/placebo. This co-BRIM study[32]: International, randomised, blinded placebo-controlled trial evaluating the benefit of trial demonstrated improved response rates and survival with combination

	therapy.

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Declaration of Interests

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Reference annotations
* *Of interest*
** *Of considerable interest*

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Table 1: Pharmacokinetics of vemurafenib and cobimetinib

	Vemurafenib[49]	**Cobimetinib**[50, 51]
Oral bioavailability	High inter-patient variability; improved with high-fat meal; high accumulation at steady state	45.9%; not impacted by food intake
Half-life	51.6 hours (5^{th}-95^{th} percentile range 29.8-115.5)	43.6 hours (range 23.1-69.6)
Volume distribution	91L (64.8% between patient variability); *in vitro* >99% protein-bound	806L; 94.8% protein-bound *in vitro*
Metabolism	CYP3A4 identified as main mechanism *in vitro*, glucuronidation and glycosylation contribute *in vivo*	CYP3A oxidation and glucuronidation by UGT2B7
Clearance	29.3L/hour; eliminated in faeces (94%) and urine (1%); probable additional biliary excretion; renal and hepatic excretion unknown	13.8L/hour; eliminated in faeces

Table 2: Summary of efficacy results from Phase I and III trials of vemurafenib with cobimetinib, as well as Phase III results of dabrafenib with trametinib

Trial Phase	Drugs tested	Number patients	Median PFS (months)	Overall response rate	Complete response rate	Median OS (months)	1 year OS
Phase 1b[28]	Vem+Cobi BRAFi naïve	63	13.7	87%	10%	Not reached	83%
	Vem+Cobi previous BRAFi	66	2.8	15%	0%	8.3	32%
Phase 3 (coBRIM)[33, 34]	Vem+Cobi	248	12.3	70%	16%	22.3	75%
	Vem+Plac	247	7.2	50%	11%	17.4	nd
Phase 3 (Combi-D)[8]	Dab+Tram	211	11.0	69	16	25.1	74%
	Dab	212	8.8	53	13	18.7	68%
Phase 3 (Combi-v)[10]	Dab+Tram	352	11.4	64	13	Not reached	72%
	Vem	352	7.3	51	8	17.2	65%

Vem+Cobi= vemurafenib and cobimetinib; Vem+Plac= vemurafenib and placebo; Dab+Tram=dabrafenib and trametinib; PFS= progression free survival; OS= overall survival

Table 3: Adverse event rates with vemurafenib and Cobimetinib compared to vemurafenib monotherapy and the combination of dabrafenib with trametinib

Adverse Events	Vemurafenib/ Cobimetinib[32]		Vemurafenib[32]		Dabrafenib/ Trametinib[8]	
	All (%)	G3/G4 (%)	All (%)	G3/G4 (%)	All (%)	G3* (%)
Any Adverse Event	95	49/13	96	49/9	87	32
Systemic						
Fever	26	2/0	22	0/0	52	7
Fatigue	32	4/0	31	3/0	27	2
Gastrointestinal						
Diarrhoea	56	6/0	28	0/0	18	<1
Nausea	40	1/0	24	1/0	20	0
Vomiting	21	1/0	13	1/0	14	<1
Skin						
Rash-General	39	5/1	35	5/0	24	0
Hyperkeratosis	10	0/0	29	2/0	6	0
Cutaneous SCCs	3	2/0	11	11/0	3	3
Musculolskeletal						
Arthralgia	32	2/0	40	5/0	16	<1
Cardiac						
Reduced Ejection Fraction	8	1/0	3	1/0	4	1
QT prolongation	4	1/0	4	1/0	nd	nd
Ophthalmic						
Retinal Detachment	8	2/<1	0	0/0	nd	nd
Laboratory Abnormalities						
Increased Creatine Kinase	31	7/4	<4	1/0	nd	nd
Increased ALT	24	11/<1	19	6/<1	10	2
Increased AST	22	8/0	13	2/<1	11	3

n/d = not documented.
*G4 not reported

Figure 1: Oncogenic signaling via the MAPK pathway