DRUP – Drug specific study manual for VEMURAFENIB + COBIMETINIB

(Zelboraf + Cotellic)

1. Drug specific in- and exclusion criteria

Vemurafenib specific criteria are highlighted in light grey.

Inclusion criteria		Yes	No	n.a.
1.	Patients must be ≥18 years of age.			
2.	Histologically-proven locally advanced or metastatic solid tumor, multiple myeloma or non-Hodgkin lymphoma, with symptomatic disease progression or progression according to RECIST-criteria after standard anti-cancer therapy, or for whom no such treatment is available or indicated.			
	a. <u>For patients with a primary brain tumor</u>: histologically confirmed recurrent or de novo primary brain tumor , with unequivocal progression after prior therapy, at least 3 months after radiotherapy (either first line chemo-radiotherapy or re-irradiation), and with stable or decreasing dosage of steroids for at least 7 days prior to the baseline MRI scan.			
3.	Presence of an oncogenic mutation that can potentially be targeted by Vemurafenib + cobimetinib (please refer to the list of drugs and acceptable profiles for further definitions). A complete sequencing report, confirming the actionable mutation has to be submitted for patient enrollment.			
4.	ECOG performance status 0-2			
5.	Patients must have normal organ and bone marrow function measured within 4 weeks prior to administration of study treatment as defined below:			
	a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L			
	b. Hemoglobin > 5.6 mmol/l			
	c. Platelet count > 75 x 10^9/L			
	d. Total bilirubin < 2 x ULN			
	e. AST (SGOT) and ALT (SGPT) < 2.5 x institutional ULN (or < 5 x ULN in patients with known hepatic metastases)			
	f. Serum creatinine ≤ 1.5 × ULN or calculated or measured creatinine clearance ≥ 50 mL/min/1.73 m^2			
6.	Objectively measurable disease (by physical or radiographic examination, according to RECIST v1.1 for patients with solid tumors, or according to IMWG, Lugano, RANO or GCIG criteria, resp., for patients with multiple myeloma, non-Hodgkin lymphoma, glioblastoma or ovarian cancer in case of CA125-based evaluation).			

Inclusion criteria	**Yes**	**No**	**n.a.**
7. A new (obtained ≤2 months before inclusion, and without any type of anti-cancer therapy within those ≤2 months) fresh frozen tumor biopsy specimen for extensive biomarker testing is mandatory before the start of treatment with a targeted agent included in the protocol. Alternatively, fresh frozen tumor tissue acquired in the context of a standard care procedure may be used, provided that no systemic anti-cancer treatment was given between the procedure and start of study treatment within DRUP. The following exceptions are made: a) An exception is made for patients with a primary brain tumor, only if the mandatory DRUP pre-treatment biopsy for biomarker analysis cannot safely be obtained: i. The fresh frozen tumor biopsy sample may be replaced by fresh frozen tumor tissue, obtained earlier from recurrent disease, as part of standard of care surgical procedure (i.e., performed at progression) ii. If no fresh frozen tumor tissue is available for NGS, and the risk of obtaining a new tumor biopsy is considered too high, no biopsy will be required. In this case, the study coordinators must be informed in advance, and there will be no reimbursement for the biopsy procedure. b) In case WGS is performed on tumor tissue outside the context of a clinical trial before inclusion, and without any type of anti-cancer therapy between the collection of tissue and inclusion in DRUP, this can replace the DRUP pre-treatment biopsy, provided that the patient gives consent to use his/her WGS data for biomarker analysis in DRUP. c) An exception is made for patients that underwent an allogeneic hematopoietic stem cell transplantation prior to study enrollment, since this will prevent a correct WGS analysis due to a mismatch between the biopsy specimen and the required blood sample.			
8. Ability to understand and the willingness to sign a written informed consent document.			
9. For orally administered drugs, the patient must be able to swallow and tolerate oral medication and must have no known malabsorption syndrome.			
10. Women of child-bearing potential and men must agree to use adequate contraception for the duration of study participation, and for six months following completion of study therapy. For women of childbearing potential: negative serum pregnancy test.			

Exclusion criteria	**Yes**	**No**	**n.a.**
1. Patients that are eligible for on-label treatment with vemurafenib or for ongoing phase 2 / 3 trials with vemurafenib are excluded from treatment with vemurafenib within the DRUP trial.			
2. Known hypersensitivity to the active substance or to any of the excipients.			
3. Corrected QT (QTc) interval ≥450 msec at baseline or history of congenital long QT syndrome.			
4. Patients with a baseline LVEF either below institutional lower limit of normal (LLN) or below 50%			
5. Ongoing toxicity > grade 2, other than alopecia.			

Exclusion criteria	**Yes**	**No**	**n.a.**
6. Patient is receiving any other anti-cancer therapy (cytotoxic, biologic, radiation, or hormonal other than for replacement). Required wash out period prior to starting study treatment is at least two weeks. An exception is made for patients suffering from CRPC, who are allowed to continue androgen deprivation therapy.			
7. Patient is pregnant or nursing.			
8. Patients with known active progressive brain metastases. Patients with previously treated brain metastases are eligible, provided that the patient has not experienced a seizure or had a clinically significant change in neurological status within the 3 months prior to registration. All patients with previously treated brain metastases must be stable for at least 1 month after completion of treatment and off steroid treatment prior to study enrollment.			
a. <u>For patients with a primary brain tumor</u>: (I) Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). EIAED are prohibited. Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization. (II) No radiotherapy within the three months prior to the diagnosis of progression. (III) No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven.			
9. Patients with clinically significant preexisting cardiac conditions, including uncontrolled or symptomatic angina, uncontrolled atrial or ventricular arrhythmias, or symptomatic congestive heart failure are not eligible.			
10. Patients with stroke (including TIA) or acute myocardial infarction within 2 months before the first dose of study treatment are not eligible.			
11. Patients with any other clinically significant medical condition which, in the opinion of the treating physician, makes it undesirable for the patient to participate in the study or which could jeopardize compliance with study requirements including, but not limited to: ongoing or active infection, significant uncontrolled hypertension, or severe psychiatric illness/social situations.			

NB Please note that official prescription instructions, as outlined in the Summary of Product Characteristics (SPC, most recent version can be downloaded from https://www.ema.europa.eu/en/medicines) and / or any other official documents concerning this drug, will always take precedence over this manual. This manual is provided for practical support; treatment can be performed according to local standard-of-care protocols.

2. Treatment schedule

	Screening (≤28 days before start)	After screening, before start	D1 of every treatment cycle (1 cycle = 28 days)	At the end of every 2nd treatment cycle	After end of treatment (≤30 days)
Concurrent meds	x		x		
Adverse events			x		
Physical exam	x		x[1,2]		
Vital signs	x		x[1]		
Performance Status	x		x[1]		
CBC w/diff, platelets	x		x[1]		
Serum chemistry	x[3]		x[3]		
Serum pregnancy test	x[7]		x[7]		
ECG	x		x[4]		
LVEF assessed by MUGA or ECHO	x		x[5]		
Vemurafenib (Zelboraf)			x (continuous dosing)		
Cobimetinib (Cotellic)			x (daily, from day 1 until day 21)		
Tumor biopsy		x[8]			x[8]
Response evaluation	x[6]			x[6]	

1. According to local standard clinical practice, or as clinically indicated.
2. Perform dermatologic evaluations for new primary cutaneous malignancies. Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances are identified, an ophthalmologic examination is recommended.
3. Including sodium, potassium, magnesium, AST, ALT, alkaline phosphatase and bilirubin. Correct electrolyte abnormalities before treatment. Other serum chemistry according to local standard clinical practice, or as clinically indicated
4. If during treatment the QTc exceeds 500 ms, vemurafenib treatment should be temporarily interrupted, electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled.
5. LVEF should be evaluated after the first month of treatment and at least every 3 months or as clinically indicated until treatment discontinuation. Patients restarting treatment with a dose reduction of cobimetinib should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated.
6. A baseline scan should be performed <28 days before start of treatment. Tumor assessments will initially be repeated every 8 weeks after treatment initiation. If the patient continues study treatment beyond 3 response evaluations (i.e., 24 weeks), response

evaluation will thereafter be performed at the end of every 3rd treatment cycle (i.e., every 12 weeks).

7. For women of child-bearing potential: serum pregnancy test should be performed.
8. After screening is positive, the mandatory DRUP pre-treatment biopsy will be obtained. After end of treatment, a post-treatment biopsy can be obtained. The post-treatment biopsy is optional.

3. Administration and starting dosage

The recommended dose of vemurafenib is 960 mg (four 240 mg tablets) orally every 12 hours with or without a meal. A missed dose can be taken up to 4 hours prior to the next dose.

The recommended dose of cobimetinib is 60 mg (3 tablets of 20 mg) once daily. Cobimetinib is taken on a 28 day cycle. Each dose consists of three 20 mg tablets (60 mg) and should be taken once daily for 21 consecutive days (Days 1 to 21-treatment period); followed by a 7-day break (Days 22 to 28-treatment break). Each subsequent cobimetinib treatment cycle should start after the 7-day treatment break has elapsed. Cobimetinib is for oral use. The tablets should be swallowed whole with water. They can be taken with or without food. If a dose is missed, it can be taken up to 12 hours prior to the next dose to maintain the once-daily regimen.

Treatment can continue until disease progression or unacceptable toxicity occurs. Do not take an additional dose if vomiting occurs after treatment administration, but continue with the next scheduled dose. Do not crush or chew the tablets.

4. How supplied

Vemurafenib is supplied as 240 mg film-coated tablets. Cobimetinib is supplied as 20 mg film-coated tablets. Drugs can be (re-)ordered by filling in the required fields in the eCRF. Drugs will be shipped to the site's pharmacy. Per shipment, sufficient drug can be ordered to treat the patient until the next response evaluation (and 1 cycle beyond for the first order, to cover the period in between response evaluation and re-supply).

5. Dose modifications for toxicity

Please refer to Summary of Product Characteristics (SPC).

6. Warnings and precautions

Adverse Events of Special Interest (AESI): the following AE's are considered AESI. Regardless of whether they meet the seriousness criteria, AESI should **always** be reported within 1 working day (using the SAE form, conform the SAE procedure):

- Any retinal vein occlusion (RVO)
- Any retinal detachment or central serous chorioretinopathy (CSCR)
- Grade ≥ 3 photosensitivity
- Grade ≥ 2 LVEF reduction
- Grade ≥ 3 QT interval prolongation

- Any cutaneous and non-cutaneous primary malignancy, including SCC, KA, BCC, and new primary melanoma
- Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin > 2× ULN (of which 35% is direct bilirubin), or treatment-emergent ALT or AST > 3 × baseline value in combination with clinical jaundice)

VEMURAFENIB

Hypersensitivity reactions: serious hypersensitivity reactions, including anaphylaxis and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome) have been reported. Severe hypersensitivity reactions may include Stevens-Johnson syndrome, generalised rash, erythema or hypotension. In patients who experience severe hypersensitivity reactions or DRESS Syndrome, vemurafenib treatment should be permanently discontinued.

QT Prolongation: monitor ECG and electrolytes before and during treatment. Withhold vemurafenib for QTc of 500 ms or greater. Correct electrolyte abnormalities and control for cardiac risk factors for QT prolongation.

Serious Ophthalmologic Reactions: monitor for signs and symptoms of uveitis.

New Malignancies: perform dermatologic evaluations prior to initiation of therapy, 2 months while on therapy, and for up to 6 months following discontinuation of vemurafenib for the development of Non-Cutaneous Squamous Cell Carcinoma (non-cuSCC). Manage with excision and continue treatment without dose adjustment. New Non-Cutaneous Squamous Cell Carcinoma: Evaluate for symptoms or clinical signs of new noncutaneous SCC before initiation of treatment and periodically during treatment. Other Malignancies: Monitor patients closely for signs or symptoms of other malignancies.

Pancreatitis: pancreatitis has been reported in vemurafenib-treated subjects. Unexplained abdominal pain should be promptly investigated (including measurement of serum amylase and lipase). Patients should be closely monitored when re-starting vemurafenib after an episode of pancreatitis.

Hepatotoxicity: monitor liver enzymes and bilirubin before initiating vemurafenib and monthly during treatment, or as clinically indicated. Laboratory abnormalities should be managed with dose reduction, treatment interruption or with treatment discontinuation.

Photosensitivity: all patients should be advised to avoid sun exposure while taking vemurafenib. Patients should be advised to wear protective clothing and use a broad spectrum Ultraviolet A (UVA)/Ultraviolet B (UVB) sunscreen and lip balm (Sun Protection Factor ≥ 30) when outdoors to help protect against sunburn. For photosensitivity grade 2 (intolerable) or greater, dose modifications are recommended.

Interactions: avoid concomitant use of strong CYP3A4 inhibitors (including boceprevir, cyclosporine, clarithromycin, erythromycin, indinavir, Iitraconazole, ketoconazole, quinidine, posaconazol, ritonavir, saquinavir, telaprevir and voriconazol) and strong CYP3A4 and / or Pgp inductors (including carbamazepine, rifampicin and St John's Wort).

COBIMETINIB

Serous retinopathy (fluid accumulation within the layers of the retina): has been observed in patients treated with MEK-inhibitors, including combimetinib. Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances are identified, an ophthalmologic examination is recommended. If serous retinopathy is diagnosed, Cobimetinib treatment should be withheld until visual symptoms improve to Grade ≤1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (please refer to SPC for further details).

Left ventricular dysfunction: LVEF should be evaluated before initiation of treatment to establish baseline values, then after the first month of treatment and at least every 3 months or as clinically indicated until treatment discontinuation. Decrease in LVEF from baseline can be managed using treatment interruption, dose reduction or with treatment discontinuation. All patients restarting treatment with a dose reduction of Cotellic should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated.

Liver laboratory abnormalities: can occur when cobimetinib is used in combination with vemurafenib and with vemurafenib as a single agent. Grade 3 liver laboratory abnormalities should be managed with vemurafenib treatment interruption or dose reduction. Manage Grade 4 liver laboratory abnormalities with treatment interruption, dose reduction or with treatment discontinuation of both cobimetinib and vemurafenib.

Diarrhea: should be managed with anti-diarrheal agents and supportive care. For Grade ≥3 diarrhea that occurs despite supportive care, Cobimetinib and vemurafenib should be withheld until diarrhea has improved to Grade ≤1. If Grade ≥3 diarrhea recurs, the dose of cobimetinib and vemurafenib should be reduced.

Lactose intolerance: this medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, congenital lactase deficiency or glucose-galactose malabsorption should consult with their physician and discuss whether the benefits outweigh the risks on an individual basis.

Drug-drug interactions: concurrent use of strong CYP3A inhibitors during treatment with cobimetinib should be avoided. Caution should be exercised if a moderate CYP3A4 inhibitor is co-administered with cobimetinib. If concomitant use with a strong or moderate CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety and dose modifications applied if clinically indicated. Concomitant use of moderate and strong CYP3A inducers (e.g. carbamazepine, rifampicin, phenytoin, and St. John’s Wort) should be avoided, since a a reduction in cobimetinib exposure is likely.