DRUP – Drug specific study manual for REGORAFENIB (Stivarga)

1. Drug specific in- and exclusion criteria

Regorafenib 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 regorafenib (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 0-1			
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 *			
* Transfusion to meet these inclusion criteria will not be allowed			
d. Total bilirubin < 1.5 x ULN			
e. AST (SGOT) and ALT (SGPT) < 2.5 x institutional ULN (or < 5 x ULN in patients with known hepatic metastases)			
f. Alkaline phosphatase ≤2.5 x ULN (≤5x ULN for patients with liver involvement of their cancer and /or bone metastases)			
g. Serum creatinine ≤ 1.5 × ULN or calculated or measured creatinine clearance ≥ 50 mL/min/1.73 m^2			
h. Lipase ≤ 1.5 x ULN			
i. INR ≤1.5 x ULN and PTT or APTT ≤1.5 x ULN for patients not receiving therapeutic anticoagulation (e.g., heparin). Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate if no underlying abnormality in coagulation parameters exists per medical history. If a subject is taking warfarin or heparin with stable PT-INR at baseline, close monitoring of PT-INR and aPTT should be performed ≥1 times/week until PT-INR and aPTT are stable as compared with a pre-dose measurement (defined by the local standard of care).			
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 allogenic 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 four months following completion of study therapy.			
11. Women of childbearing potential must have a blood or urine pregnancy test performed a maximum of 7 days before start of study treatment, and a negative result must be documented before start of study treatment.			

Exclusion criteria	Yes	No	n.a.
1. Patients that are eligible for on-label treatment with regorafenib or for ongoing phase 2 / 3 trials with regorafenib are excluded from treatment with regorafenib within the DRUP trial.			
2. Known hypersensitivity to the active substance or to any of the excipients.			

Exclusion criteria	**Yes**	**No**	**n.a.**
3. Concomittant use of strong CYP3A4 inhibitors (eg, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole) or strong CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort).			
4. Any of the following infections:			
a. Known history of human immunodeficiency virus (HIV) infection.			
b. Active hepatitis B or C, or chronic hepatitis B or C requiring treatment with antiviral therapy.			
c. Ongoing infection > Grade 2 NCI CTCAE			
5. Persistent proteinuria > 3.5 g/24 hours measured by urine protein-creatinine ratio from a random urine sample (≥ grade 3, NCI-CTCAE v 4.0).			
6. Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.			
7. Major surgical procedure or significant traumatic injury within 28 days before start of study medication.			
8. Non-healing wound, non-healing ulcer, or non-healing bone fracture.			
9. Patients with evidence or history of any bleeding diathesis, irrespective of severity.			
10. Patients who had prior extensive radiotherapy in the abdomen or in the lungs or in more than 3 vertebrae in the spine.			
11. Any hemorrhage or bleeding event ≥CTCAE grade 3 within 4 weeks prior to the start of study medication.			
12. History of organ allograft.			
13. Previous or concurrent cancer that is distinct in primary site or histology from the studied cancer within 5 years prior to randomization, except for curatively treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumors.			
14. Ongoing toxicity > grade 2, other than alopecia.			
15. 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.			
16. Patient is pregnant or nursing.			
17. 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. For patients with a primary brain tumor: (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.			

Exclusion criteria	**Yes**	**No**	**n.a.**
18. 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.			
19. Patients with known left ventricular ejection fraction (LVEF) < 40% are not eligible.			
20. Patients with an arterial or venous thrombotic or embolic events, such as cerebrovascular accident (including TIA), deep vein thrombosis or pulmonary embolism or acute myocardial infarction within 6 months before the first dose of study treatment are not eligible (except for adequately treated catheter-related venous thrombosis occurring ≥1 month before the start of study medication).			
21. Uncontrolled hypertension (systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg), despite optimal medical management.			
22. 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	1 cycle = 28 days				At the end of every 2nd treatment cycle	After end of treatment (≤30 days)
			D1 of every Cycle	C1 and C2, D8	C1 and C2, D15	C1 and C2, D22		
Concurrent meds	x		x					
Adverse events			x					
Physical exam	x		x[1]					
Vital signs	x		x[1,2]	x[2]	(x[2])	(x[2])		
Performance Status	x		x[1]					
CBC w/diff, platelets	x		x		x			
Serum chemistry	x[3]		x[3]		x[3]			
Serum pregnancy test	x[12]							
Thyroid function tests	x[4]		x[4]					
Coagulation panel	x[5]		x[5]		x[6]			
Urinalysis by dipstick	x[7]		x[8]		x[8]			
Tumor biopsy		x[11]						x[11]
Regorafenib (Stivarga)			x[9] (continuous dosing from D1 until D21)					
Response evaluation	x[10]						x[10]	

1. According to local standard clinical practice, or as clinically indicated.
2. Blood pressure monitoring required weekly for first 6 weeks post-first dose.
3. Including eGFR, electrolyte panel, ASAT, ALAT and bilirubin. Liver enzymes must be monitored at least once every two weeks during the first 2 cycles of treatment with regorafenib (ie, on Days 1 and 15 of Cycles 1 and 2 [±3 days]). Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated.
4. If the TSH is abnormal, free T3 and free T4 will be measured.
5. Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate if no underlying abnormality in coagulation parameters exists per medical history. If a subject is taking warfarin or heparin with stable PT-INR at baseline, close monitoring of PT-INR and aPTT should be performed ≥1 times/week until PT-INR and aPTT are stable as compared with a pre-dose measurement (defined by the local standard of care).

6. Only if subject is maintained on warfarin or heparin.
7. Microscopic analysis and proteinuria quantification if indicated.
8. If the urine dipstick test shows a change from normal that is clinically significant, full urinalysis, including microscopic analysis, creatinine and proteinuria quantification, and creatinine/protein ratio, should be performed.
9. Regorafenib is taken once daily for 3 weeks followed by 1 week off therapy.
10. 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).
11. If screening is positive, a mandatory DRUP pre-treatment biopsy will be performed. After end of treatment a post-treatment biopsy can be obtained. The post-treatment biopsy is optional.
12. During screening, a serum test should be performed within 7 days before the first dose of regorafinib for all female participants of childbearing potential.

3. Administration and starting dosage

The recommended dose of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle.

If a dose is missed, then it should be taken on the same day as soon as the patient remembers. The patient should not take two doses on the same day to make up for a missed dose. In case of vomiting after regorafenib administration, the patient should not take additional tablets.

Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs.

4. How supplied

Regorafenib is supplied as 40 mg 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).

Each bottle contains 28 film-coated tablets. Store in the original package in order to protect from moisture. Keep the bottle tightly closed and keep the desiccant in the bottle. Once the bottle is opened the medicinal product has shown to be stable for 7 weeks. Thereafter, the medicinal product is to be discarded.

5. Dose modifications for toxicity

Please refer to Summary of Product Characteristics (SPC).

6. Warnings and precautions

Hepatic effects: abnormalities of liver enzymes (ALT, AST, and bilirubin) have been frequently observed in subjects treated with regorafenib. Severe liver function test abnormalities (Grades 3-4) and hepatic dysfunction with clinical manifestations (including fatal outcomes) have been reported in a small proportion of subjects. It is recommended to perform liver function tests (ALT, AST, and bilirubin) before initiation of treatment with regorafenib and to monitor closely during treatment.

Infections: regorafenib has been associated with an increased risk of infections, some with fatal outcome (for further details see SPC section 4.8).
In case of deterioration of infections, interruption of treatment with regorafenib should be considered.

Hemorrhage: regorafenib has been associated with an increased incidence of hemorrhagic events, some of which were fatal. Blood counts and coagulation parameters should be monitored in subjects with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g., warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding. In the event of severe bleeding necessitating urgent medical intervention, permanent discontinuation of regorafenib should be considered.

Cardiac ischemia and infarction: subjects with a history of ischemic heart disease should be monitored for clinical signs and symptoms of myocardial ischemia. In subjects who develop cardiac ischemia and/or infarction, interruption of regorafenib is recommended until resolution. The decision to re-initiate regorafenib therapy should be based on careful consideration of the potential benefits and risks of the individual subject. Regorafenib should be permanently discontinued if there is no resolution.

Posterior Reversible Encephalopathy Syndrome (PRES): signs and symptoms of PRES include seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging. In subjects developing PRES, discontinuation of regorafenib, along with control of hypertension and supportive medical management of other symptoms is recommended.

Arterial hypertension: blood pressure should be controlled prior to initiation of treatment with regorafenib. It is recommended to monitor blood pressure and to treat hypertension in accordance with standard medical practice. In cases of severe or persistent hypertension despite adequate medical management, regorafenib should be temporarily interrupted and/or the dose reduced at the discretion of the treating physician. In case of hypertensive crisis, regorafenib should be discontinued.

Gastrointestinal perforation and fistula: discontinuation of regorafenib is recommended in subjects developing gastrointestinal perforation or fistula.

Wound healing complications: since products with anti-angiogenic properties may suppress or interfere with wound healing, temporary interruption of regorafenib is recommended for precautionary reasons in subjects undergoing major surgical procedures. The decision to resume treatment with regorafenib following major surgical intervention should be based on clinical judgment of adequate wound healing.

Dermatological toxicity: hand-foot skin reaction (HFSR) or palmar-plantar erythrodysesthesia syndrome and rash represent the most frequently observed dermatological ADRs with regorafenib. Measures for the prevention of HFSR include control of calluses and use of shoe cushions and gloves to prevent pressure stress to soles and palms. Management of HFSR may include the use of keratolytic creams (e.g., urea-, salicylic acid-, or alpha hydroxyl acid-based creams applied sparingly only on affected areas) and moisturizing creams (applied liberally) for symptomatic relief. Dose reduction and/or temporary interruption of regorafenib, or in severe or persistent cases, permanent discontinuation of regorafenib should be considered.

Safety warning for liver cirrhosis: patients with cirrhosis of the liver should be screened according to local standard clinical practice and then treated for esophageal varices before starting treatment with regorafenib.

Biochemical and metabolic laboratory test abnormalities: electrolyte and metabolic abnormalities are generally of mild to moderate severity, not associated with clinical manifestations, and do not usually require dose interruptions or reductions. It is recommended to monitor biochemical and metabolic parameters during regorafenib treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Dose interruption or reduction, or permanent discontinuation of regorafenib should be considered in case of persistent or recurrent significant abnormalities.

Inhibitors of CYP3A4 and UGT1A9, and inducers of CYP3A4: strong CYP3A4 inhibitors (eg, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole) or strong CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort) are not permitted. Co-administration of a strong UGT1A9 inhibitor (e.g. mefenamic acid, diflunisal, and niflumic acid) during regorafenib treatment should be avoided, as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.

UGT1A1 and UGT1A9 substrates: co administration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates.

Breast cancer resistance protein and P-glycoprotein substrates: co-administration of regorafenib may increase the plasma concentrations of concomitant BCRP substrates, such as methotrexate, or P-glycoprotein substrates, such as digoxin.

CYP isoform-selective substrates: regorafenib may be given concomitantly with substrates of CYP2C8, CYP2C9, CYP3A4, and CYP2C19 without a clinically meaningful drug interaction.

Antibiotics and bile salt-sequestering agents: co-administration may interfere with the enterohepatic circulation of regorafenib and may result in a decreased regorafenib exposure.