DRUP – Drug specific study manual for Pemigatinib (Pemazyre®)

1. Drug specific in- and exclusion criteria

Pemigatinib 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, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia, with symptomatic or radiological 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 gene alteration that can potentially be targeted by pemigatinib (please refer to the list of drugs and acceptable profiles for further definitions). A complete sequencing report, confirming the actionable gene alteration has to be submitted for patient enrollment.			
4. ECOG performance status 0-2			
5. Patients must have acceptable 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			
g. Serum phosphate ≤ ULN			
h. Serum calcium inside of the institutional normal range or serum albumin-correct calcium inside of the institutional normal range when serum albumin is outside of the institutional normal range.			
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 and T-cell prolymphocytic leukemia, primary brain tumors 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 or other tumor types with only intracerebral lesions, 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. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last dose of study drug and must refrain from donating sperm during this period. Female participants who are WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose on day 1 and must agree to take appropriate precautions to avoid pregnancy from screening through 30 days (1 menstrual cycle) after the last dose of study pemigatinib and must refrain from donating oocytes during this period.			

Exclusion criteria	Yes	No	n.a.
1. Patients that are eligible for on-label treatment with pemigatinib or for ongoing phase 2 / 3 trials with pemigatinib are excluded from treatment with pemigatinib within the DRUP trial.			
2. Prior treatment with regorafenib.			

Exclusion criteria	Yes	No	n.a.
3. Any concomitant use of an FGFR inhibitor (other than pemigatinib) or any other investigational study drug for any indication.			
4. Known hypersensitivity to the active substance or to any of the excipients.			
5. Use of any potent CYP3A4 inhibitors or inducers or moderate CYP3A4 inducer within 14 days or 5 half-lives (whichever is longer) before the first dose of study drug. Moderate CYP3A4 inhibitors are not prohibited but should be avoided.			
6. Ongoing toxicity ≥ grade 2, other than alopecia or grade 2 peripheral neuropathy.			
7. 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.			
8. Patient is pregnant or nursing.			
9. Patients with 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.			
<u>*For patients with a primary brain tumor*</u>*:* *a. 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.* *b. No radiotherapy within the three months prior to the diagnosis of progression.* *c. No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven.*			
10. 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.			
11. Patients with known left ventricular ejection fraction (LVEF) < 40% are not eligible.			
12. Patients with stroke (including TIA) or acute myocardial infarction within 3 months before the first dose of study treatment are not eligible.			
13. History of calcium and phosphate homeostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissues (exception: commonly observed calcifications in soft tissues such as the skin, kidney tendon, or vessels due to injury, disease, or aging in the absence of systemic mineral imbalance).			
14. Current evidence of clinically significant corneal (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, and keratoconjunctivitis) or retinal disorder (including but not limited to macular/retinal degeneration, diabetic retinopathy, and retinal detachment) as confirmed by ophthalmologic examination.			
15. History of hypovitaminosis D requiring supraphysiologic doses (eg, 50,000 UI/weekly) to replenish the deficiency. Vitamin D supplements are allowed.			

Exclusion criteria	**Yes**	**No**	**n.a.**
16. 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 = 21 days)	At the end of every 3rd treatment cycle	After end of treatment (≤30 days after stop)
Concurrent meds	x		x		
Adverse events			x		
Physical exam	x		x[1]		
Vital signs	x		x[1]		
Performance Status	x		x[1]		
Hb, neutrophil count, platelets	x		x[1]		
Serum chemistry and endocrinology	x[3]		x[3]		
Serum phosphate			x[2]		
Serum pregnancy test	x[6]				
Comprehensive eye examination	x[4]			x[4]	x[4]
Tumor biopsy		x[7]			x[7]
Pemigatinib			x (continuous dosing for 2 weeks, followed by 1 week off)		
Response evaluation	x[5]			x[5]	

1. According to local standard clinical practice, or as clinically indicated.
2. Serum phosphate should be checked at D8 and D15 of cycle 1 and at D1 of every subsequent cycle. Based on duration and severity of hyperphosphatemia reduce the dose or permanently discontinue pemigatinib (see section 4).
3. Serum chemistry should include: Albumin, Alkaline phosphatase, ALAT, ASAT, Amylase, Bicarbonate or CO_2, Blood urea nitrogen or urea, Calcium, Chloride, Creatinine, Glucose,

Lactate dehydrogenase, Lipase, Magnesium, Phosphate, Potassium, Sodium, Total bilirubin, Direct bilirubin (if total bilirubin is elevated above ULN), Total protein, Uric acid, Vitamin D & PTH

4. A comprehensive eye examination should be performed by a qualified ophthalmologist at screening, once every 3 cycles (± 7 days, starting at Cycle 3), at EOT, and as clinically indicated. The eye examination should include a visual acuity test, slit-lamp examination, fundoscopy with digital imaging, and OCT. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.
5. Baseline scan should be performed ≤28 days before start of treatment. Tumor assessments will initially be repeated every 9 weeks after treatment initiation. If the patient continues study treatment beyond 3 response evaluations (i.e., 27 weeks), response evaluation will thereafter be performed at the end of every 12 weeks.
6. During screening, a serum test should be performed within 7 days before the first dose of abemaciclib for all female participants of childbearing potential.
7. Tumor biopsy: after screening is positive, a mandatory DRUP pre-treatment biopsy should be taken. After termination of DRUP treatment, a post-treatment biopsy can be taken. The post-treatment biopsy is optional.

2. Administration and starting dosage

The recommended starting dose of pemigatinib is 13.5 mg (three 4.5 mg tablets) once daily, on a schedule of 2 weeks on treatment followed by 1 week off, to comprise a complete cycle of 3 weeks. Pemigatinib may be taken with food or between meals. If a dose is missed by >4 hours or if the patient vomits after taking pemigatinib, the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity.

3. How supplied

Pemigatinib is supplied as tablets (4.5 mg tablets, 14 counts). 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).

4. Dose modifications for toxicity

Please refer to Summary of Product Characteristics (SPC) for pemigatinib related toxicities and specific instructions.

<u>Hyperphosphatemia</u>

In all patients, a low-phosphate diet should be initiated when serum phosphate level is > 5.5 mg/dL and adding a phosphate-lowering therapy should be considered when level is > 7 mg/dL. The dose of phosphate-lowering therapy should be adjusted until serum phosphate level returns to < 7 mg/dL.

Prolonged hyperphosphatemia can cause precipitation of calcium-phosphate crystals that can lead to hypocalcaemia, soft tissue mineralization, muscle cramps, seizure activity, QT interval prolongation, and arrhythmias.
Discontinuing phosphate-lowering therapy and diet should be considered during pemigatinib treatment breaks or if serum phosphate level falls below normal range. Severe hypophosphatemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and hemolytic anemia.
Dose modifications for hyperphosphatemia are shown in table 2.

Concomitant use of pemigatinib with CYP3A4 inhibitors

Pemigatinib is predominantly metabolized by CYP3A4. There is an expected 50% increase in exposure in patients who concomitantly use CYP3A4 moderate inhibitors. Therefore the use of moderate CYP3A4 inhibitors should be avoided; however, if unavoidable, the pemigatinib dose should be reduced from 13.5 mg to 9 mg or from 9 mg to 4.5 mg. If concomitant use of a moderate CYP3A inhibitor is discontinued, the pemigatinib dose can be increased (after 3 plasma half-lives of the CYP3A inhibitor) to the dose that was administered before starting the moderate inhibitor. The use of potent CYP3A4 inhibitors and inducers and moderate CYP3A4 inducers is prohibited. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.
Careful monitoring, especially in relation to safety, is required when pemigatinib is concomitantly administered with OCT2 substrates such as dofetilide and metformin, mild or moderate CYP3A4 inhibitors or mild CYP3A4 inducers, and proton pump inhibitors.

Concomitant use of pemigatinib with Calcium-based phosphate-binders

Calcium-based phosphate-binding medications should not be used due to a concern for soft tissue mineralization.

Serous retinal detachment

Pemigatinib can cause serous retinal detachment reactions, which may present with symptoms such as blurred vision, visual floaters, or photopsia.
A comprehensive eye examination should be performed by a qualified ophthalmologist at screening, once every 3 cycles (± 7 days, starting at Cycle 3), at EOT, and as clinically indicated. The eye examination should include a visual acuity test, slit-lamp examination, fundoscopy with digital imaging, and OCT. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.
Dose modifications for serous retinal detachment are shown in table 3.

Management of toxicities

Dose modifications or interruption of dosing should be considered for the management of toxicities.

Pemigatinib dose reductions levels are summarised in table 1.

Table 1: Recommended pemigatinib dose reduction levels

Dose	Dose reduction levels	
	First	**Second**
13.5 mg taken orally once daily for 14 days followed by 7 days off therapy	9 mg taken orally once daily for 14 days on, followed by 7 days off therapy	4.5 mg taken orally once daily for 14 days on, followed by 7 days off therapy

Treatment should be permanently discontinued if patient is unable to tolerate 4.5 mg pemigatinib once daily.

Dose modifications for hyperphosphatemia are provided in table 2.

Table 2: Dose modifications for hyperphosphatemia

Adverse reaction	**Pemigatinib dose modification**
> 5.5 mg/dL - ≤ 7 mg/dL	• Pemigatinib should be continued at current dose.
> 7 mg/dL - ≤ 10 mg/dL	• Pemigatinib should be continued at current dose, phosphate lowering therapy should be initiated, serum phosphate should be monitored weekly, dose of phosphate lowering therapy should be adjusted as needed until level returns to < 7 mg/dL. • Pemigatinib should be withheld if levels do not return to < 7 mg/dL within 2 weeks of starting a phosphate lowering therapy. Pemigatinib and phosphate-lowering therapy should be restarted at the same dose when level returns to < 7 mg/dL. • Upon recurrence of serum phosphate at > 7 mg/dL with phosphate-lowering therapy, pemigatinib should be reduced 1 dose level.
> 10 mg/dL	• Pemigatinib should be continued at current dose, phosphate lowering therapy should be initiated, serum phosphate should be monitored weekly and dose of phosphate lowering therapy should be adjusted as needed until level returns to < 7 mg/dL. • Pemigatinib should be withheld if levels continue > 10 mg/dL for 1 week. Pemigatinib and phosphate-lowering therapy should be restarted 1 dose level lower when serum phosphate is < 7 mg/dL. • If there is recurrence of serum phosphate > 10 mg/dL following 2 dose reductions, pemigatinib should be permanently discontinued.

Dose modifications for serous retinal detachment are provided in table 3.

Table 3: Dose modifications for serous retinal detachment

Adverse reaction	Pemigatinib dose modification
Asymptomatic	• Pemigatinib should be continued at current dose. Monitoring should be performed as described above.
Moderate decrease in visual acuity (best corrected visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline); limiting instrumental activities of daily living	• Pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib should be resumed at the next lower dose level. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered based on clinical status.
Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or > 3 lines decreased vision from baseline up to 20/200); limiting activities of daily living	• Pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib may be resumed at 2 dose levels lower. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered, based on clinical status.
Visual acuity worse than 20/200 in affected eye; limiting activities of daily living	• Pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib may be resumed at 2 dose levels lower. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered, based on clinical status.

Dose modification for other toxicities are provided in table 4

Table 4: Dose modifications for other toxicities

Adverse Event	Action Taken
Chemistry	
• AST and/or ALT is > 5.0 × ULN.	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 or baseline except by approval of the medical monitor. **Step 2:** Restart study drug at same dose. If assessed as related to study drug, restart study drug at next lower dose; monitor as clinically indicated.
Other toxicities	
• Any Grade 1 or Grade 2 toxicity.	Continue study drug treatment and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until toxicity resolves to ≤ Grade 1 or baseline. **Step 2:** Restart study drug at same dose. If assessed as related to study drug, restart study drug at next lower dose; monitor as clinically indicated.

Adverse Event	Action Taken
• Any recurrent Grade 3 toxicity after 2 dose reductions.	Discontinue study drug administration and follow-up per protocol. (Exceptions require approval of sponsor.)
• Any other Grade 4 toxicity. • QT/QTc to > 500 ms or to > 60 ms over baseline[a].	Discontinue study drug administration and follow-up per protocol.

5. Warnings and precautions

Hyperphosphatemia
Hyperphosphatemia is a pharmacodynamic effect expected with pemigatinib administration. Prolonged hyperphosphatemia can cause precipitation of calcium-phosphate crystals that can lead to hypocalcaemia, soft tissue mineralization, anemia, secondary hyperparathyroidism, muscle cramps, seizure activity, QT interval prolongation, and arrhythmias. Soft tissue mineralization, including cutaneous calcification and calcinosis, have been observed with pemigatinib treatment. Recommendations for management of hyperphosphatemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required (see section 4). Phosphate-lowering therapy was used by 19% of patients during treatment with pemigatinib.

Hypophosphatemia
Discontinuing phosphate-lowering therapy and diet should be considered during pemigatinib treatment breaks or if serum phosphate level falls below normal range. Severe hypophosphatemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and hemolytic anemia. Hypophosphatemia reactions were ≥ Grade 3 in 14.3 % of participants. None of the events were serious, led to discontinuation or to dose reduction. Dose interruption occurred in 1.4% of participants. For patients presenting with hyperphosphatemia or hypophosphatemia, additional close monitoring and follow-up is recommended regarding dysregulation of bone mineralization.

Serous retinal detachment
Pemigatinib can cause serous retinal detachment reactions, which may present with symptoms such as blurred vision, visual floaters, or photopsia. This can moderately influence the ability to drive and use machines.
A comprehensive eye examination should be performed by a qualified ophthalmologist at screening, once every 3 cycles (± 7 days, starting at Cycle 3), at EOT, and as clinically indicated. The eye examination should include a visual acuity test, slit-lamp examination, fundoscopy with digital imaging, and OCT. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.
Careful consideration should be taken with patients that have clinically significant medical eye disorders, such as retinal disorders, including but not limited to, central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, and previous retinal detachment.

Dry eyes

Pemigatinib can cause dry eyes. Patients should use ocular demulcents, in order to prevent or treat dry eye, as needed.

Embryo-fetal toxicity

Based on the mechanism of action and findings in an animal reproduction study, pemigatinib can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the fetus. Women of childbearing potential should be advised to use effective contraception during treatment with pemigatinib and for 1 week after the last dose. Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with pemigatinib and for at least 1 week after the last dose.

Blood creatinine increase

Pemigatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine; this may occur due to inhibition of renal transporters OCT2 and MATE1 and may not affect glomerular function. Within the first cycle, serum creatinine increased (mean increase of 0.2 mg/dL) and reached steady state by day 8, and then decreased during the 7 days off therapy. Alternative markers of renal function should be considered if persistent elevations in serum creatinine are observed.

Combination with proton pump inhibitors

Concomitant use of pemigatinib with proton pump inhibitors should be avoided.

Combination with moderate CYP3A4 inhibitors

Concomitant use of pemigatinib with moderate CYP3A4 inhibitors requires dose adjustment (see section 4). Patients should be advised to avoid eating grapefruit or drinking grapefruit juice while taking pemigatinib.

Combination with strong or moderate CYP3A4 inducers

Concomitant use of pemigatinib with strong or moderate CYP3A4 inducers is not recommended.

CNS metastasis

Since untreated or progressing brain/CNS metastasis were not allowed in the study, efficacy in this population has not been evaluated and no dose recommendations can be made, however the blood-brain barrier penetration of pemigatinib is expected to be low.

Contraception

Based on findings in an animal study and its mechanism of action, pemigatinib can cause fetal harm when administered to a pregnant woman.

Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last dose of study drug and must refrain from donating sperm during this period.

Female participants who are WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose on day 1 and must agree to take appropriate precautions to avoid pregnancy from screening through 30 days (1 menstrual cycle) after the last dose of study pemigatinib and must refrain from donating oocytes during this period.

6. Special Populations

Elderly patients

The dose of pemigatinib is the same in elderly patients as younger adult patients.

Renal impairment

Dose adjustment is not required for patients with mild, moderate renal impairment or End Stage Renal Disease (ESRD) on haemodialysis. For patients with severe renal impairment, the dose of patients who are taking 13.5 mg pemigatinib once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg pemigatinib once daily should be reduced to 4.5 mg once daily.

Hepatic impairment

Dose adjustment is not required for patients with mild or moderate hepatic impairment. For patients with severe hepatic impairment, the dose of patients who are taking 13.5 mg pemigatinib once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg pemigatinib once daily should be reduced to 4.5 mg once daily.

Paediatric population

The safety and efficacy of pemigatinib in patients less than 18 years of age have not been established. No data are available.