Selected chapters from study protocol:

A randomized phase II study to explore the efficacy and feasibility of upfront bi-monthly rotations between Everolimus and Pazopanib with sequential treatment of first line Pazopanib and second line Everolimus until progression in patients with advanced or metastatic clear cell renal cancer.

Subtitle: Rotating Pazopanib & Everolimus to avoid resistance. (the ROPETAR trial)

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1 Study objectives

1.1 Primary objective
The primary objective is to assess the progression-free survival (PFS) of patients who receive bi-monthly rotations of pazopanib and everolimus versus patients who receive pazopanib as a first line treatment.

PFS is defined as progressive disease per RECIST 1.1 or death whichever comes first in arm A (alternating schedule) and after pazopanib monotherapy in arm B. Comparing time to first PD with time to first PD.

Patients who have not progressed or died at the date of the analysis cut-off or when they receive any further anticancer therapy will have their disease status censored at the time of the last adequate tumor assessment before the cut-off date or the anticancer therapy date.

For the primary analysis, the PFS will be based on the independent (local) radiological data according to RECIST 1.1(1).

1.2 Secondary objectives
The secondary objectives are time to second progression or death: defined as time to progressive disease per RECIST 1.1 on everolimus monotherapy (when PD after 8 weeks pazopanib) or pazopanib monotherapy (when PD after 8 weeks everolimus) as second line treatment in arm A and time to progressive disease on everolimus in arm B. “Baseline” tumor assessment for this secondary endpoint is the assessment which showed first progressive disease which resulted in cessation of the alternating regimen in arm A, and pazopanib in arm B. Comparing time to 2nd PD with time to 2nd PD, overall survival, quality of life, toxicity of randomized patients receiving treatment as defined in arm A compared to arm B.

Other secondary objectives include pharmacodynamic measurements and pharmacokinetic assessments at the switch of pazopanib and everolimus and vice versa.

To develop biomarkers that may predict responsiveness to either of the agents used.

Quality of life assessments and Common Toxicity Criteria will be used.

Interim safety analysis will be performed. An Independent Data and Safety Monitoring Committee (IDSMC) will be asked to determine the safety.
2 Design

2.1 Screening phase
Written informed consent prior to performance of study-specific procedures or assessments will be obtained.
Evaluations will be performed within 28 days prior to the first dose of study treatment (Day 28-day 1). Screening evaluations include:
1. the administration of patient informed consent.
2. a review of inclusion/exclusion criteria.
3. a physical examination including:
   a. neurological examination (by treating physician).
   b. vital signs, ECG.
   c. current concomitant medications.
   d. documentation of relevant medical history/current medical conditions.
   e. documentation of prior anti-neoplastic therapies.
4. confirmation of RCC diagnosis and extent of disease (sites of metastatic disease):
   a. CT or MRI with contrast of chest/abdomen/pelvis and/or
   b. bone scan in case of clinical suspicion of bone metastases.
   c. brain MRI or CT scan in case of clinical suspicion of central nervous system (CNS) metastases or leptomeningeal carcinomatosis.
   d. blood and urine laboratory tests (including Urine Protein to Creatinine Ratio).
   e. WHO performance status and MSKCC(2) prognostic criteria.
   f. soluble biomarkers (10ml).
5. Patients with increased risk for developing hepatitis should be tested for hepatitis B and C at baseline. Patients with increased risk include patients with multiple sexual partners, (previous) intravenous drug users, and people with a history of multiple transfusions.

2.2 Treatment phase
This study does not have a fixed treatment duration. Patients in the experimental arm (Arm A) will receive the alternating study regimen starting with pazopanib until first disease progression per RECIST 1.1 followed by everolimus or pazopanib monotherapy until second progression or until unacceptable toxicity is observed, or patient withdrawal for any other reason.
In the comparative arm (Arm B) patients will receive a standard regimen of pazopanib until progression, followed thereafter by everolimus until progression.

The initiation of any non-protocol specific anti-tumor treatment or surgery is considered an indication of disease progression and should be recorded appropriately. Information on drug exposure will be collected in the CRF.

Patients will receive their first dose of study drugs preferably on day 1 but at least within one week after randomization. If unexpected circumstances impede the patient to comply with the established visit schedule, the site can re-schedule the visit ± 3 to 4 days of the planned visit date. The reason(s) for any visit adjustments or treatment delays will be recorded in the CRF.

Scheduled bi-weekly visits will be scheduled in the first two cycles (16 weeks), thereafter monthly (every 28 days) visits will be scheduled.
Tumor assessments, by the local radiologist will be performed every 8 weeks (±1 week) until disease progression after both agents.
4 weeks after ceasing study medication for any reason an end-of-treatment visit will be scheduled. After the end-of-treatment visit patients will be followed for survival up to 1 year after the last patient is randomized in the study.
Clinical suspicion of disease progression at any time requires a physical examination and radiological documentation to be performed promptly rather than waiting for the next scheduled radiological assessment.
At every visit during the study including the end-of-treatment visit patients will be assessed for AEs, SAEs and also for hypertension, proteinuria, gastrointestinal perforations, any major injury or surgical procedure and arterial thromboembolic events, irrespective of causal relationship.

With regard to patients developing hypertension during the treatment the algorithm as described for pazopanib and for everolimus should be followed until blood pressure returns to within normal range (≤ 150/90 mmHg). Patients who have ongoing proteinuria or who experience new proteinuria, will be monitored by 24-hour urine collection as described in previous mentioned algorithms.

Patients who have ongoing wound healing complications at the end-of-treatment visit or who experience a new wound healing event during the follow-up period will have their wound healing complications monitored every 4 weeks until the event(s) has resolved.

2.3 Study population
The study will enroll 100 patients who have advanced and/or metastatic clear cell cancer of the kidney. To achieve the inclusion of 100 patients this study will be performed as a multicenter trial.

Data will be collected on patient characteristics including demographic information (age, sex, race, and ethnicity), overall and specific medical history, and any other assessments that are done for the purpose of determining eligibility for inclusion in the study. Specific medical history should include the following, if applicable:
- Low hemoglobin (requiring transfusions or erythropoietin treatment), platelet transfusion.
- Nicotine abuse.
- Body weight loss in the last 6 months.
- Hematuria or proteinuria.
- Hypertension.
- Cancer history and extent of cancer, prior anticancer therapies.
- Heart condition (NYHA criteria).

In pre-menopausal women, a pregnancy test will only be performed 7 days prior to randomization and will not be repeated after the patient has started study treatment.
3 Statistical considerations

The primary objective of this study is to assess whether the experimental arm (alternating pazopanib and everolimus) yields anti-tumor activity deemed worthwhile to be further explored in a randomized phase III study. The primary endpoint will be the progression-free survival after treatment start (PFS).

Stratification: for randomization and efficacy analyses, patients will be stratified according to the Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria (favorable vs. intermediate vs. poor risk groups, based on Karnofsky performance status, hemoglobin and corrected serum calcium, LDH and time from initial diagnosis < 1 year).

3.1.1 Sample size

The primary endpoint is PFS. PFS curves will be constructed by means of the Kaplan-Meier technique, and analysed using a log-rank test according to the intention-to-treat principle (ie according to randomization). A total of 100 patients will be randomized in this study, 50 in each arm. The expected accrual period is two years. From a previous series it is estimated that the 1 year PFS in the standard arm will be 50%. If patients are followed until a total of 60 events (progression or death) are observed roughly one year after the last randomization assuming exponentially), the study will have 90% power to detect an increase in 1 year PFS of 30% (ie 50% vs. 80%), and a 80% power to detect an increase of 22% (ie 50% to 72%) (alpha = 0.05, 2 tailed test).
4 Eligibility

4.1 Inclusion criteria
- Subjects must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up.
- Age ≥ 18 years.
- Histologically confirmed diagnosis of progressive clear cell renal cell cancer defined as >10% of the tumor cells having the clear cell phenotype.
- Locally advanced (defined as disease not amenable to curative surgery or radiation therapy) or metastatic RCC (equivalent to Stage IV RCC according to AJCC staging).
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
- Measurable disease.
- No prior systemic anti-cancer treatment against clear cell renal cell cancer.
- Adequate organ system function as defined in Table 1.

4.1.1 Table 1: Definitions for Adequate Organ Function

<table>
<thead>
<tr>
<th>System</th>
<th>Laboratory Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count (ANC)</td>
<td>≥1.5 X 10^9/L</td>
</tr>
<tr>
<td>Hemoglobin(^a)</td>
<td>≥9 g/dL (5.6 mmol/L)</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100 X 10^9/L</td>
</tr>
<tr>
<td>Prothrombin time (PT) or international normalized ratio (INR)(^b)</td>
<td>≤1.2 X ULN</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (aPTT)</td>
<td>≤1.2 X ULN</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>≤1.5 X ULN</td>
</tr>
<tr>
<td>Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)(^c)</td>
<td>≤2.5 X ULN or ≤5.0 x ULN in case of liver metastases</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>≤1.5 mg/dL (133 μmol/L)</td>
</tr>
<tr>
<td>Or, if &gt;1.5 mg/dL: Calculated creatinine clearance (ClCR)</td>
<td>≥50 mL/min</td>
</tr>
<tr>
<td>Urine Protein to Creatinine Ratio(^d)</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

- a. Subjects may not have had a transfusion within 7 days of screening assessment.
- b. Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.
- c. Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN (upper limit of normal) are not permitted.
- d. If UPC ≥1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1 g to be eligible.

- A female is eligible to enter and participate in this study if she is of: Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had:
• A hysterectomy.
• A bilateral oophorectomy (ovariectomy).
• A bilateral tubal ligation.
• Is post-menopausal.

Subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years in age, OR in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

Subjects using HRT must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT

Childbearing potential, including any female who has had a negative serum pregnancy test within 14 days prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

• Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product.
• Oral contraceptive, either combined or progestogen alone.
• Injectable progestogen.
• Implants of levonorgestrel.
• Estrogenic vaginal ring.
• Percutaneous contraceptive patches.
• Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year.
• Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject.
• Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository).

Procedures conducted as part of the subject’s routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.

4.2 Exclusion criteria

• Prior malignancy.
  Note: Subjects who have had another malignancy and have been disease-free for 5 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.
• History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medication for 3 months prior to first dose of study drug. Screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only in case of clinical suspicion or if the subject has a history of CNS metastases.
• Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to:
  • Active peptic ulcer disease.
  • Known intraluminal metastatic lesion/s with risk of bleeding.
  • Inflammatory bowel disease (e.g. ulcerative colitis, Crohn’s disease), or other gastrointestinal conditions with increased risk of perforation.
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment.
- Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to:
  - Malabsorption syndrome.
  - Major resection of the stomach or small bowel.
- Presence of uncontrolled infection.
- Known past or present infection with Hepatitis B virus (HBV), Hepatitis C virus (HCV) or Human Immunodeficiency Virus (HIV).
- Corrected QT interval (QTc) > 480 msecs using Bazett’s formula.
- History of one or more of the following cardiovascular conditions within the past 6 months:
  - Cardiac angiolplasty or stenting.
  - Myocardial infarction.
  - Stable or unstable angina pectoris.
  - Coronary artery bypass graft surgery.
  - Symptomatic peripheral vascular disease.
  - Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA).
- Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥160 mmHg or diastolic blood pressure (DBP) of ≥90 mmHg].

**Note:** Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. BP must be re-assessed on two occasions that are separated by a minimum of 1 hour; on each of these occasions, the mean (of 3 readings) SBP / DBP values from each BP assessment must be <160/90 mmHg in order for a subject to be eligible for the study. **For treatment suggestions see section 5.6.2. “Anti hypertensive medication”**.

- History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.
  **Note:** Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible.
- Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major).
- Evidence of active bleeding or bleeding diathesis.
- Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels.
- Hemoptysis in excess of 2.5 mL (or one half teaspoon) within 8 weeks of first dose of study drug.
- Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject’s safety, provision of informed consent, or compliance to study procedures.
- Unable or unwilling to discontinue use of prohibited medications or modify the dosing of interacting drugs for at least 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study.
- Pregnant or lactating female.
  **Note:** Lactating females who discontinue nursing prior to the first dose of study drug and agree to refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug are eligible.
- Treatment with any of the following anti-cancer therapies:
  - Radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of pazopanib OR
  - Chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy.
5 Drug related topics

5.1 Everolimus dosing instructions
Commercially available packs of everolimus (trade name Afinitor) contain 30 everolimus tablets of 10 mg strength, blister-packed under aluminum foil in units of 10 tablets, 3 foils per package - and are dosed on a basis of 10 mg per day. If a patient is enrolled in the control arm (arm B), everolimus will be prescribed and dispensed on an outpatient basis, until the end-of-treatment as part of regular care. In the experimental arm A, everolimus will be supplied by the WIN-O free of charge via the pharmacy of the participating hospital.

In this trial the starting dose will be everolimus 10mg qd.

The storage conditions for everolimus will be provided on commercial label, tablets should be kept in the blister packs until the time of administration as it is both hygroscopic and light-sensitive. Patients will be provided with an adequate supply of everolimus for self administration at home. The investigator should instruct the patient to take everolimus exactly as prescribed. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded in the CRF.

Patients will be instructed to take one 10 mg tablet of everolimus orally with a glass of water, once daily at the same time each day in the morning, after a light low-fat meal. Any dietary habits around the time of everolimus intake should be as consistent as possible throughout the study. If vomiting occurs, no attempt should be made to replace the vomited dose unless the everolimus tablet is clearly visible.

Patients will keep a diary of their everolimus intake at home. At clinic visits, compliance should be verified by the investigator’s staff by viewing this diary. Patient compliance will be registered. The patient will continue to take everolimus until disease progression; a rotation to pazopanib should be made according to protocol, major toxicity or withdrawal from the study for any reason. The maximum allowed time of study medication interruption is 3 weeks.

5.2 Everolimus-specific toxicities
Adverse events most frequently observed with everolimus (incidence ≥ 10%) are rash, stomatitis/oral mucositis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, asthenia, cough, peripheral edema, dry skin, pruritis, epistaxis, dyspnea, and infections. Overall, the most frequently observed laboratory abnormalities include anemia, lymphocytopenia, neutropenia, thrombocytopenia, hyperglycemia, hypercholesterolemia, and/or hypertriglyceridemia, increased creatinine, increased ALT/AST, and decreased phosphate. The majority of these AEs have been of mild to moderate severity (CTC Grade 1-2) (3).

Management of stomatitis/oral mucositis/mouth ulcers
Stomatitis/oral mucositis/mouth ulcers due to everolimus should be treated using local supportive care.
1. For mild toxicity (Grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash four times a day or more until resolution.
2. For more severe toxicity (Grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients cannot maintain adequate oral alimentation), suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracainehydrochloride, menthol, or phenol) with or without topical corticosteroids (such as triamcinolone oral paste 0.1% (Kenacort-A in Orabase))
3. Agents containing hydrogen peroxide, iodine, or thyme tend to worsen mouth ulcers.
4. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents should be avoided in all patients due to their strong inhibition of everolimus metabolism, leading to higher everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

Management of hyperlipidemia and hyperglycemia
Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Grade 2 hypercholesterolemia (> 7.75 mmol/L) or Grade 2 hypertriglyceridemia (>2.5 x ULN) should be treated with a HMG-CoA reductase inhibitor or appropriate lipid-lowering medication. Patients
should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis. Grade 3 hyperglycemia has been observed in patients receiving everolimus therapy. In many cases, the affected patients had an abnormal fasting glucose at baseline. Optimal glucose control should be achieved before starting on everolimus and monitored during therapy.

Management of diarrhea

Appearance of diarrhea attributed to everolimus toxicity may be treated with loperamide.

Management of non-infectious pneumonitis

Both asymptomatic radiological changes (Grade 1 = radiological lung changes only) and symptomatic non-infectious pneumonitis (Grade 2 = not interfering with activities of daily living) or Grade 3 (interfering with activities of daily living and oxygen indicated) have been noted in patients receiving everolimus therapy. If non-infectious pneumonitis develops, consultation with a pulmonologist is recommended. Concurrent administration of corticosteroids and everolimus should be avoided. Temporarily discontinuation of everolimus less than three weeks is allowed. Record the non-infectious pneumonitis in the CRF. The radiologist will review CT scans and chest X-rays of respective patients.

5.2.1 Table 2: Everolimus dose adjustments in case of pneumonitis

<table>
<thead>
<tr>
<th>Worst Grade Pneumonitis</th>
<th>Required Investigations</th>
<th>Management of Pneumonitis</th>
<th>EVEROLIMUS Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>CT scans with lung windows. Repeat at least every 6 weeks until return to within normal limits.</td>
<td>No specific therapy is required.</td>
<td>Administer 100% of everolimus dose.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider bronchoscopy. *</td>
<td>Consider Corticosteroids. When corticosteroids are prescribed everolimus should be interrupted.</td>
<td>Re-start everolimus when recovery to ≤ Grade 1. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 3 weeks. Everolimus dose cannot be escalated.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended and a biopsy and/or bronchoalveolar lavage is required.</td>
<td>Prescribe corticosteroids if infective origin is ruled out. Hold treatment with everolimus.</td>
<td>Hold treatment until recovery to ≤ Grade 1. May restart protocol treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>CT scan with lung windows and required pulmonary function testing, if possible, including: spirometry, DLCO, and room air O2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy with biopsy and/or BAL is recommended if possible.</td>
<td>Consider corticosteroids if infective origin is ruled out.</td>
<td>Discontinue treatment.</td>
</tr>
</tbody>
</table>

5.3 Everolimus dosing modifications

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on everolimus. The guidelines set forth in Table 3 and 4 should be followed: If treatment is interrupted due to toxicity, everolimus should not be resumed until recovery to ≤ Grade 1, then reintroduce everolimus at the initial dose or lower dose level depending on toxicity type and Grade (Table 4). These changes must be recorded on the Dosage Administration Record CRF.

5.3.1 Table 3: Guidelines for everolimus dose reduction in case of toxicity

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (starting dose)</td>
<td>10 mg, p.o. daily</td>
</tr>
</tbody>
</table>
Decrease 1 dose level  5 mg, p.o. daily
Decrease 2 dose level  5 mg, p.o. every other day

If a patient has already decreased 2 dose levels and no further dose reduction is possible, those requiring a third dose reduction must discontinue everolimus. Table 4 provides the procedure for dose modification and re-initiation of everolimus in the event of toxicities suspected to be related to the study drug.

### 5.3.2 Table 4: Criteria for dose modification in case of suspected everolimus toxicity and re-initiation of everolimus treatment

<table>
<thead>
<tr>
<th>Non hematological toxicity</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 (except pneumonitis – see Table 2)</td>
<td>If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt everolimus until recovery to ≤ Grade 1. Then reintroduce everolimus at same dose. If event returns to Grade 2, then interrupt everolimus until recovery to ≤ Grade 1. Then reintroduce everolimus at the lower dose level.</td>
</tr>
<tr>
<td>Grade 3 (except hyperlipidemia*)</td>
<td>Interrupt everolimus until recovery to ≤ Grade 1. Then reintroduce everolimus at the lower dose level. For pneumonitis consider the use of a short course of corticosteroids.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue everolimus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematological toxicity</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 Thrombocytopenia (platelets &lt;75, ≥ 50 x10⁹/L)</td>
<td>Interrupt everolimus until recovery to ≤ Grade 1 (&gt;75 x10⁹/L). Then reintroduce everolimus at initial dose. If thrombocytopenia again returns to Grade 2, interrupt everolimus until recovery to ≤ Grade 1. Then reintroduce everolimus at the lower dose level.</td>
</tr>
<tr>
<td>Grade 3 Thrombocytopenia (platelets &lt;50, ≥ 25 x10⁹/L)</td>
<td>Interrupt everolimus until recovery to ≤ Grade 1 (platelets ≥ 75 x10⁹/L). Then resume everolimus at one dose level lower. If Grade 3 thrombocytopenia recurs, discontinue everolimus.</td>
</tr>
<tr>
<td>Grade 4 Thrombocytopenia (platelets &lt; 25 x10⁹/L)</td>
<td>Discontinue everolimus.</td>
</tr>
<tr>
<td>Grade 3 Neutropenia (neutrophils &lt;1, ≥0.5 x10⁹/L)</td>
<td>Interrupt everolimus until recovery to ≤ Grade 1 (neutrophil ≥ 1.5 x 10⁹/L). Then resume everolimus at the initial dose. If ANC again returns to Grade 3, hold everolimus until the ANC ≥ 1.5 x 10⁹/L. Then resume everolimus dosing at the lower dose level. Discontinue patient from study therapy for a third episode of Grade 3 neutropenia.</td>
</tr>
<tr>
<td>Grade 4 Neutropenia (neutrophils &lt; 0.5 x10⁹/L)</td>
<td>Interrupt everolimus until recovery to ≤ Grade 1 (neutrophil ≥ 1.5 x 10⁹/L). Then resume everolimus at the lower dose level. If ≥ Grade 3 neutropenia occurs despite this dose reduction, discontinue everolimus.</td>
</tr>
<tr>
<td>Grade 3 febrile neutropenia (not life-threatening)</td>
<td>Interrupt everolimus until resolution of fever and neutropenia to ≤ Grade 1. Hold further everolimus until the ANC ≥ 1,500/mm³ and fever has resolved. Then resume everolimus at the lower dose level. If febrile neutropenia recurs, discontinue everolimus.</td>
</tr>
<tr>
<td>Grade 4 febrile neutropenia (life-threatening)</td>
<td>Discontinue everolimus</td>
</tr>
<tr>
<td>Any hematological or non-hematological toxicity requiring interruption for ≥ 3 weeks</td>
<td>Discontinue everolimus</td>
</tr>
</tbody>
</table>

*Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies.

### 5.4 Pazopanib dosing instructions

Pazopanib monohydrochloride (trade name Votrient) is supplied as a series of aqueous film-coated tablets containing 200mg and 400mg of the freebase:

- **Dose** 200 mg **Description** Capsule-shaped, pink, film-coated tablet **Imprint** GS JT, in bottles containing 30 or 90 tablets each.
- **Dose** 400 mg **Description** Capsule-shaped, white, film-coated tablet **Imprint** GS UHL, in bottles containing 30 or 60 tablets each.

In this trial the starting dose will be pazopanib 800mg qd.
Pazopanib should be taken orally without food at least one hour before or two hours after a meal. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively constant. If a dose is missed, the subject should take the dose as soon as possible, but not if there are less than 12 hours before the next dose is due. If the next dose is due in less than 12 hours, the subject should skip the missed dose and take the next dose as scheduled. If vomiting occurs after taking pazopanib another dose is not permitted on that day. The subject should resume taking pazopanib at the next scheduled dose. If vomiting persists, the subject should be instructed to notify the investigator.

If a patient should use pazopanib the upcoming month according to the protocol pazopanib will be prescribed and dispensed on an outpatient basis, until the end-of-treatment. Patients will keep a diary of their pazopanib intake at home. At clinic visits, compliance should be verified by the investigator's staff by viewing this diary. Patient compliance will be registered.

5.5 Pazopanib-specific toxicities

Frequently observed side effects of pazopanib (>10%) are diarrhea, fatigue, hypertension, hair colour changes, anorexia, nausea and/or vomiting, fatigue, abdominal pain and headache.

The most common biochemical abnormalities include AST/ALT elevation, hyperbilirubinemia, alkaline phosphatase elevation, lymphopenia, neutropenia, thrombocytopenia and anemia(4).

Management of diarrhea

Appearance of diarrhea attributed to pazopanib toxicity may be treated with loperamide, probiotics or metamucil.

Hypertension

Hypertension has been observed in 47% of patients treated with pazopanib(4). Patients included should have acceptable controlled blood pressure at baseline defined as systolic blood pressure (SBP) of ≤ 160 mmHg or diastolic blood pressure (DBP) of ≤ 90 mmHg. Hypertension occurring in the course of the treatment should be treated according to the Dose Modification Algorithms for hypertension in table 5.

Nausea and/or vomiting

Anti-emetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT antagonists) may be administered prophylactically in the event of nausea.

Abdominal pain and headache

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate. Although acetaminophen at doses of ≤2 g/day is permitted, it should be used with caution in subjects with impaired liver function.

Hepatotoxicity

Modest to severe hepatotoxicity has been observed. Around 90% of transaminases elevations occur in the first 18 weeks of treatment. As a consequence transaminases should be monitored at least monthly. When a separate LFT panel is tested, it should include the following: ALT, AST, alkaline phosphatase, GGT, and total bilirubin. A direct bilirubin level should be obtained if the total bilirubin level is greater than 2x upper limit of normal (ULN). In case of elevated serum alanine or aspartate transaminases (ALT, AST) and bilirubin dosing modifications should be made following the dose modification algorithm for hepatotoxicity in Table 6.

Other possible side effects

Other possible side effects include proteinuria, hemorrhage /bleeding, venous thrombosis (DVT, PE), arterial thrombosis/ischemia, thrombocytopenia, anemia and prolongation of QTc Interval. Electrocardiographic parameters with a particular focus on QTc interval duration will be performed if clinically indicated.

Adverse event specific dose modification algorithms as provided in this protocol should be followed.
Any other clinically significant adverse event should be graded according to the NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4).

### 5.6 Pazopanib dosing Modifications

Recommendations for investigational product dose interruptions/modifications in case of specific treatment-emergent AEs are provided in Table 5.

#### 5.6.1 Table 5: Pazopanib dose modification algorithms in case of specific treatment-emergent AEs

<table>
<thead>
<tr>
<th>AE Terms &amp; Descriptions</th>
<th>Dose Modification Algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
</tr>
</tbody>
</table>
| (A). Asymptomatic and persistent SBP of \( \geq 150 \) mmHg and \(< 170 \) mmHg, or DBP \( \geq 90 \) mmHg, or a clinically significant increase in DBP of \( \geq 20 \) mmHg. | Step 1. Continue investigational product (pazopanib) at the current dose.  
Step 2. Adjust current or initiate new antihypertensive medication(s). For suggestions see section 5.6.2. “Anti hypertensive medication”.  
Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve acceptable controlled blood pressure (BP). If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B). |
| (B). Asymptomatic SBP \( \geq 170 \) mmHg, or DBP \( \geq 110 \) mmHg, or failure to achieve acceptable-controlled BP within 2 weeks in scenario (A). | Step 1. Consider reducing or interrupting pazopanib, as clinically indicated.  
Step 2. Adjust current or initiate new antihypertensive medication(s).  
Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP.  
Step 4. Once BP is well-controlled, restart pazopanib dose-reduced by 200 mg if it was interrupted. |
| (C). Symptomatic hypertension or recurring SBP \( \geq 170 \) mmHg, or DBP \( \geq 110 \) mmHg, despite modification of antihypertensive medication(s) | Step 1. Interrupt pazopanib  
Step 2. Adjust current or initiate new antihypertensive medication(s).  
Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended.  
Step 4. Once BP is well-controlled, restart pazopanib dose-reduced by 200 mg. |
| (D). Refractory hypertension unresponsive to above interventions. | Discontinue pazopanib and continue follow-up per protocol. |
| **Proteinuria**          |                             |
| 24-hr urine protein \( \geq 3 \) grams | Step 1. Interrupt pazopanib.  
Step 2. Test weekly the 24-hour urine protein until the level is < 3 grams. Then, restart pazopanib dose reduced by 200 mg.  
Step 3. If 24-hour urine protein \( \geq 3 \) grams recurs, repeat Steps 1 and 2.  
Step 4. If 24-hour urine protein \( \geq 3 \) grams recurs and the pazopanib dose can no longer be reduced, discontinue pazopanib and continue follow up per protocol. |
| **Hemorrhage/Bleeding**  |                             |
| Grade 1                  | Continue pazopanib with current dose; monitor as clinically indicated. |
| Grade 2                  | Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue pazopanib and continue follow-up per protocol. Otherwise, |
### AE Terms & Descriptions

<table>
<thead>
<tr>
<th>terme</th>
<th>Dose Modification Algorithms</th>
</tr>
</thead>
</table>
| Dose Modification Algo | interrupt pazopanib until the AE resolved to ≤ Grade 1.  
Step 2. Restart pazopanib; consider reducing dose and monitor as clinically indicated. |

Grade 3 or 4, or  
Recurrent ≥ Grade 2 event after dose interruption/reduction. | Discontinue pazopanib and continue with follow-up per protocol. |

### Venous Thrombosis (DVT, PE)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose Modification Algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Continue pazopanib with same dose; initiate and monitor anticoagulation as clinically indicated.</td>
</tr>
</tbody>
</table>

| Grade 3 | Step 1. Interrupt pazopanib.  
Step 2. Initiate and monitor anticoagulation as clinically indicated.  
Step 3. Resume pazopanib at reduced dose only if all of the following criteria are met:  
- The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one week.  
- No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. |

Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in pazopanib dosing (eg, re-initiating, escalating/de-escalating, or discontinuing pazopanib), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation. |

| Grade 4 and/or PE | Discontinue pazopanib and continue follow-up per protocol. |

### Arterial Thrombosis/Ischemia

| Any Grade | Discontinue pazopanib and continue follow-up per protocol. |

### Thrombocytopenia: Investigate and document underlying cause

| Grade 1 or 2 | Continue pazopanib with current dose; monitor as clinically indicated. |

| Grade 3 or 4 | Step 1. Interrupt pazopanib until toxicity resolves to ≤ Grade 2.  
Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated.  
If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4 thrombocytopenia, discontinue pazopanib and follow-up per protocol |

### Anaemia:

No specific dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above.

### Other Clinically Significant Adverse Events

| Grade 1 | Continue pazopanib; monitor as clinically indicated. |

<p>| Grade 2 or 3, if clinically significant | Step 1. Interrupt pazopanib until toxicity resolves to ≤ Grade 1. |</p>
<table>
<thead>
<tr>
<th>AE Terms &amp; Descriptions</th>
<th>Dose Modification Algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue pazopanib and continue follow-up per protocol.</td>
</tr>
</tbody>
</table>

**Prolongation of QTc Interval:** If the QTc is prolonged, the ECG should be manually read to ensure accuracy of the reading. The values below refer to manually-read ECGs.

- **QTc ≥ 480 < 500 msec**
  - Continue pazopanib; monitor as clinically indicated.

- **QTc ≥ 500 msec**
  - Discontinue pazopanib and continue follow-up per protocol.

*a.* BP defined as mean SBP < 150 mmHg and mean DBP < 90 mmHg.

*b.* AEs are graded according to NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4).

**Abbreviations:** BP, blood pressure.

### 5.6.2 Antihypertensive medication

First choice antihypertensive medication(s) for patients receiving pazopanib are Angiotensin-converting enzyme (ACE) inhibitors (e.g. Lisinopril) and selective β1 receptor blockers (e.g. Metoprolol, Carvedilol).

Dihydropyridine calcium channel blockers (e.g. Amlodipine) may worsen edema already caused by tyrosine kinase inhibitors.

Diuretics should be used with caution since they increase the risk of dehydration.

### 5.7 Pazopanib dose interruptions/modifications for hepatotoxicity

Recommendations for pazopanib dose interruptions/modifications in case of liver-related treatment-emergent AEs are provided in Table 6. As a general rule, since many subjects are taking multiple concurrent medications, it is critical to (a) do a thorough evaluation of the subject’s concurrent medications, and (b) identify and discontinue those with known hepatotoxicity and replace with a non-hepatotoxic equivalent for the same indication if necessary. Record alcohol use on the liver event alcohol intake form in the CRF. Liver dysfunction must be fully evaluated even if clinical signs and symptoms indicate progression of liver tumor lesions.
5.7.1 Table 6: Guidelines for Management of Treatment Emergent Hepatotoxicity

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose Modification Algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A). ALT of ≤ 3.0 x ULN</td>
<td>Continue pazopanib at current dose with full panel LFTs monitored as per protocol.</td>
</tr>
<tr>
<td>(B) Regarding patients without liver metastases or with liver metastases but baseline ALT ≤ 2.5 x ULN: ALT &gt; 3.0 x ULN to ≤ 8.0 x ULN without bilirubin elevation (defined as total bilirubin &lt; 2.0 x ULN or direct bilirubin ≤ 35%) and without hypersensitivity symptoms (e.g., fever, rash)</td>
<td>Liver Event Monitoring Criteria:</td>
</tr>
<tr>
<td></td>
<td>(1) Continue pazopanib at current dose levels.</td>
</tr>
<tr>
<td></td>
<td>(2) Perform the following assessments for exclusion of hypersensitivity and other contributing factors:</td>
</tr>
<tr>
<td></td>
<td>- Eosinophil count</td>
</tr>
<tr>
<td></td>
<td>- Viral serology for hepatitis A, B and C</td>
</tr>
<tr>
<td></td>
<td>(3) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.</td>
</tr>
<tr>
<td>(C). ALT &gt; 8.0 x ULN without bilirubin elevation (defined as total bilirubin &lt; 2.0 x ULN or direct bilirubin ≤ 35%) and without hypersensitivity symptoms (e.g., fever, rash)</td>
<td>1st occurrence – Liver Event Interruption Criteria:</td>
</tr>
<tr>
<td></td>
<td>(1) Interrupt pazopanib until toxicity resolves to ≤ Grade 1 or baseline. Report the event to the NKI-AVL trial Office as an SAE within 24 hours of learning of its occurrence. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments.</td>
</tr>
<tr>
<td></td>
<td>(2) Perform the following assessments for exclusion of hypersensitivity and other contributing factors:</td>
</tr>
<tr>
<td></td>
<td>- Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus (IgM antibody, heterophile antibody, or monospot testing)</td>
</tr>
<tr>
<td></td>
<td>- Liver imaging</td>
</tr>
<tr>
<td></td>
<td>(3) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.</td>
</tr>
<tr>
<td></td>
<td>(4) If the subject is benefiting from the study treatment re-treatment may be considered if ALL following criteria are met:</td>
</tr>
<tr>
<td></td>
<td>- ALT/AST reduced to Grade 1</td>
</tr>
<tr>
<td></td>
<td>- Total bilirubin &lt; 1.5 x ULN or direct bilirubin ≤ 35%</td>
</tr>
<tr>
<td></td>
<td>- No hypersensitivity signs or symptoms</td>
</tr>
<tr>
<td></td>
<td>- Subject is benefiting from therapy.</td>
</tr>
<tr>
<td>Recurrence – Liver Event Stopping Criteria:</td>
<td>Discontinue pazopanib permanently and monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.</td>
</tr>
</tbody>
</table>

a. Weekly or more frequently as clinically indicated
### Liver Event Stopping Criteria:

1. **Discontinue pazopanib immediately; report the event to the NKI-AVL trial office as an SAE within 24 hours of learning of its occurrence.** Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries and liver event follow up assessments.

2. **Consult a gastroenterologist / hepatologist and perform the following assessments to identify potential co-factors:**
   - Eosinophil count
   - Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus (IgM antibody, heterophile antibody, or monospot testing)
   - Anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody
   - Serum creatinine phosphokinase for possible muscle injury caused LFT elevation
   - Liver imaging
   - Consider toxicological blood screen for possible contributing chemical/medical entities

3. **Monitor subject closely for clinical signs and symptoms; record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form. Perform full panel LFTs weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.**

---

### For isolated total bilirubin elevation without concurrent ALT increases (defined as ALT <3 X ULN).

1. **Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Pazopanib inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury.**

2. **If bilirubin is >2 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If the bilirubin is predominantly indirect (unconjugated), continue pazopanib at the same dose. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.**

---

**Abbreviations:**
- ALT alanine aminotransferase; AST aspartate aminotransferase; CRF case report form; pazopanib; LFT liver function tests; SAE serious adverse event; ULN upper limit of normal
5.8 Interruption and/or discontinuation (withdrawal) of treatment

Patients may voluntarily withdraw from the study or be taken off study at the discretion of the investigator at any time for any reason beneficial to his/her wellbeing. If a patient requires a dose delay of his or her medication > 21 days, then the patient must be discontinued from the study.

- If such withdrawal occurs, or if the patient fails to return for follow-up visits or tumor assessments until the start of another anticancer therapy after the patient stops study treatment, the investigator must determine the primary reason for a patient’s withdrawal from the study and record this information in the CRF. All data generated up to the time of discontinuation from the study will be analyzed and the reason(s) for discontinuation will be recorded. The investigator or his/her designee will also complete the end-of-treatment visit evaluations and complete the CRF indicating the date and reason for stopping the study drug.

- For patients who are lost to follow-up, the investigator should document in the patients’ source documents, steps taken to contact the patient, dates of telephone calls, registered letters, etc.

- Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. If a patient has discontinued the study treatment due to an unacceptable adverse drug reaction or an abnormal laboratory value, he/she should have the reason for discontinuation be recorded as due to adverse drug reaction or an abnormal laboratory value.

- During the follow-up period, AEs and SAE information will be collected and recorded in the CRF. During the follow-up period, irrespective of causal relationship: hypertension, proteinuria, wound healing complications, gastrointestinal perforation, surgical procedure, major injury, and arterial thromboembolic events will be followed up and recorded. If the patient is unable to return to the clinic, the investigator or his/her designee will contact the patient or caregiver to collect this information.

- Data collection will continue on all patients who discontinue from study treatment for any reason other than tumor progression or withdrawal of informed consent until the start of another anticancer therapy or progressive disease is observed.

- The investigator or his/her designee will collect information on the initiation of additional anticancer therapy until the end of study. All new anticancer therapies after the last dose of study treatment will be recorded in the CRF. This information may be obtained during a telephone call and will be recorded in the source documents as well as in the CRF.

- The investigator or his/her designee will collect survival information on all patients every 2 months after the patient’s end-of-treatment visit up to 1 year after the last patient is randomized to the trial. Survival information may be obtained during a telephone call and will be recorded in the source documents as well as in the CRF.
6 Assessments

6.1 Radiological assessment of tumor
Tumor response and disease progression will be assessed 8-weekly using RECIST 1.1(1) To ensure a valid comparison of tumor data and uniformity in the assessment of tumor response during the study, the following procedure must be implemented at the study center:

- All lesions identified at baseline (target and non-target) will be reassessed using the same method (CT scan with contrast or MRI with contrast) throughout the course of the study.
- All CT/MRIs scans, brain MRIs or CT scans, and bone scans obtained on all patients enrolled at the center should be reviewed by the local radiologist who together with the local investigator will determine the local assessment of response and progression.
- The local radiologist will be blinded to the patient’s treatment assignment.

*Chest/Abdomen/Pelvis CT or MRI with contrast*
A CT scan with contrast or MRI with contrast of the Chest/Abdomen and Pelvis will be performed at screening ≤ 28 days prior to the first dose of study treatment. Tumor response will be assessed every 8 weeks (±1 week) from randomization until progression or start of new anticancer therapy. Patients who are allergic/sensitive to the radiographic contrast media used in CT scans and MRIs may have a CT scan of the chest without contrast or an MRI of the abdomen and pelvis without contrast. All patients should have at least one measurable disease lesion by CT scan or MRI. It is important to have the results from the last CT or MRI prior to the start of the next planned tumor evaluation.

*Bone Scan*
A bone scan will be performed at ≤ 28 days prior to the start of study treatment when clinically indicated or necessary for response evaluation according RECIST guidelines. Follow up bone scans will be performed according to the patient’s tumor assessment schedule (8 weeks ± 1 week) from randomization until second progression if indicated. If bone lesions are not detected at baseline and the patient develops symptoms or signs of bone disease, a bone scan will be performed as clinically indicated and then followed according to the patient’s tumor assessment schedule.

*Measurement of disease*
Disease lesions will be accurately measured using RECIST 1.1 (www.recist.com)(1). The following events will be additionally registered:

- If a lesion separates, the longest diameter of the resulting sub-lesions should be measured separately and the sum of all sub-lesions should be documented as measurement for the lesion. In addition, a comment must be added to the RECIST 1.1 Comments CRF to indicate that a lesion separated into two or more sub-lesions.
- If lesions become confluent, measure and record the longest diameter of the resulting mass. In addition, a comment must be added to the RECIST 1.1 Comments CRF to indicate that lesions merged into one lesion.
- If a very small lesion cannot be reliably measured because of its size, it is recommended to enter the minimum lesion size (i.e., 5 mm for spiral CT). In other cases where the lesion cannot be reliably measured for reasons other than its size (i.e., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.
- A target lesion that resolves from baseline must be assigned a size of 0 mm when documenting on the patient’s RECIST 1.1 CRFs.

6.2 Response
Response will be measured according RECIST 1.1(1).

*Evaluation of target lesions:*

**Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
**Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

**Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

**Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

### 6.3 Survival assessments

After the end-of-treatment visit, all patients will have survival assessments every 2 months up to 1 year after the last patient is randomized to the study.

### 6.4 Patient-reported outcomes

The **FKSI-DRS** measures in a validated way the most important disease-related symptoms associated with advanced kidney cancer. The symptoms covered by the 9-item FKSI-DRS include fatigue, pain, weight loss, dyspnea, cough, fever and hematuria. A difference of 2-3.0 points is suggested to correspond to a meaningful difference in treatment effects using the 9 question tool.

The **EORTC QLQ-C30** questionnaire evaluates the patient’s symptoms, function and quality of life and was selected because of its proven ability to measure the impact of cancer therapies on patients’ day to day lives. It contains 30 items and is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, social and cognitive functioning), three symptom scales (fatigue, pain, nausea, and vomiting), a global health status/QoL scale, and six single items (dyspnea, diarrhea, constipation, anorexia, insomnia and financial impact). Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. Each item has 4 response categories (1=Not at all, 2=A little, 3=Quite a bit, 4=Very much) with the higher number representing a worse outcome.

Questionnaires should be administered prior to patients being scanned or informed about their disease status. Both questionnaires will be completed by the patient pre-dose of any study drug at every bi-monthly visit and at the end-of-treatment visit.
Data management and statistical methods

7.1  Efficacy Outcome Analysis

*Analysis populations:*
The data from all centers will be pooled and summarized with respect to demographic and baseline characteristics and efficacy and safety observations. Exploratory analyses will be performed using descriptive statistics. Data will be presented into the following populations for analysis:

The **Full Analysis Set (FAS)** consists of all randomized patients. Following the intent-to-treat Principle, patients are analyzed according to the treatment and stratum they were assigned to at randomization.

The **Per Protocol population (PP)** consists of all patients from the Full Analysis Set population without any major protocol deviations who are evaluable for efficacy and have completed a minimum exposure requirement. However, if a patient progressed, discontinued for adverse event or died before the minimum exposure requirement could be met, or before he/she could become evaluable for efficacy, that patient will still be included in the Per Protocol Set. Patients will be evaluable for efficacy if they have a best overall response assessment different from ‘Unknown’ according to the RECIST 1.1 evaluation criteria. The minimum exposure requirement is defined in general as having a relative dose intensity over the first month of treatment of at least 50%. The dose intensity requirement applies to all compounds in the study treatment.

The **Safety population (SAF)** consists of all patients who received at least one dose of study medication (i.e. one dose of any compound of the study treatment) and with a valid postbaseline safety assessment. Patients are analyzed according to the treatment received.

*Analysis:*
The treatment effect on PFS of the experimental arm (Arm A) compared to the standard arm (Arm B) will be calculated. PFS curves will be constructed by means of the Kaplan-Meier technique, and analysed using a log-rank test according to the intention-to-treat principle (ie according to randomization). PFS curves will be displayed by treatment group, overall and by strata, according to the Kaplan-Meier product-limit method. The resulting median PFS time will be given with 95% confidence intervals.

The primary analysis will be performed in the FAS population. In addition, it will be repeated as supportive analysis, using the Per Protocol population.

The analyses of all **secondary endpoints** will be performed in the FAS population
Supportive secondary analyses will be performed on all available events as per local review.

7.2  Interim analysis
An interim safety analysis will be performed by the IDSMB.

7.3  Safety evaluation
The assessment of safety will be based mainly on the frequency of adverse events, on the number of laboratory values that fall outside of pre-determined ranges and on the central radiology assessment of pneumonitis. All safety outputs will use the safety population. The safety summary tables will include only assessments collected no later than 28 days after study treatment discontinuation. All safety assessments will be listed and those collected later than 28 days after study treatment discontinuation will be flagged.

**(S)AEs** will be summarized by presenting the number and percentage of patients having at least one AE, and having at least one AE in each body system/primary system organ class, and for each preferred term using Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4). A subject with multiple occurrences of an AE will be counted only once in the AE category. Separate AE summaries will be presented by primary system organ class, preferred term, and maximum CTC grade.
A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. The frequency of CTC grade 3 and 4 AEs will be summarized separately. Any information collected (e.g. CTC grades, relatedness to study drug, action taken etc.) will be listed as appropriate.

In addition, the incidence of *pneumonitis adverse events* will be summarized by preferred term for each treatment group. Treatment arms will be compared with respect to the number (%) of patients with evidence of radiological lung changes at baseline, post baseline and newly occurred or worsened cases as detected on Chest CT Scans or MRIs.

*Laboratory data* will be summarized by presenting shift tables using CTC grades (screening to most extreme post-screening value), by presenting summary statistics of raw data and change from screening values (means, medians, standard deviations) and by the flagging of CTC grades in data listings.

*Data from other tests* (e.g., electrocardiogram, vital signs, special tests) will be listed and any other information collected will be listed as appropriate.

### 7.4 Patient-reported outcomes

The compliance to the schedule of administration of both questionnaires, FKSI-DRS and QLQ-C30, will be summarized by treatment group, at baseline and in time. Furthermore, the amount and distribution of missing data will be explored by treatment group and in time.

The primary endpoint for the analyses of patient-reported outcomes will be the Disease-Related Symptoms of the FKSI (FKSI-DRS). The main secondary endpoints of patient reported outcomes will be the physical functioning (PF, 5 items) and the Global health status / QoL scale (QL) scores of the EORTC QLQ-C30. The statistical analysis will include:

- Change in means over time of the FKSI-DRS and EORTC QLQ-C30 will be reported per treatment arm.
- The time to definitive deterioration by 10% of the PF and the QL scale of the EORTC QLQ-C30 and FKSI-DSR (other levels of deterioration (e.g., 5%, 20%) will also be explored). The time to definitive worsening is calculated from the date of randomization.

### 7.5 End of study

The study will end 1 year after randomization of the last subject.
8 References


