NOVARTIS

Clinical Development

Pazopanib (VOTRIENT®)

Oncology Clinical Trial Protocol CPZP034A2410 / NCT03200717

A prospective international multicenter phase II study to evaluate the efficacy, safety and quality of life of oral daily pazopanib in patients with advanced and/or metastatic renal cell carcinoma after previous therapy with checkpoint inhibitor treatment

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Document type	Amended Protocol Version (Clean)
EUDRACT number	2017-000708-10
Version number	02
Development phase	II
Document status	Final
Release date	14-Sep-2020

Template version 15-Jan-2017

[redacted]

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List of abbreviations

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical
BP	Blood pressure
CBR	Clinical benefit rate
[redacted]	[redacted]
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CR	Complete response
CRF	Case Report/Record Form
CSR	Clinical study report
CT	Computerized tomography
CYP3A4	Cytochrome P450 3A4
DBP	Diastolic blood pressure
DDI	Drug Drug Interaction
DILI	Drug-induced liver injury
DOR	Duration of response
DVT	Deep Venous Thrombosis
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
ESMO	European Society of Medical Oncology
EU	European Union
EuroQol	EuroQol Group
FAS	Full Analysis Set
FDA	Food and Drug Administration
FKSI-DRS	Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms
[redacted]	[redacted]
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HFS	Hand-foot syndrome
HR	Hazard ratio
HSV	Herpes simplex virus
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors

[redacted]

IEC	Independent Ethics Committee
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
INR	International normalized ratio
IO	Immuno-oncology
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
[redacted]	[redacted]
LFT	Liver function tests
LPFV	Last patient first visit
MAA	Marketing authorization application
mRCC	Metastatic renal cell carcinoma
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	Mechanistic Target Of Rapamycin
MUGA	Multigated acquisition scan
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
OATP1B1	Organic Anion Transporter Protein B1
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PFS	Progression-Free Survival
PPS	Per-Protocol Set
PR	Partial response
PRO	Patient reported outcomes
QTcF	QTc corrected by Fridericia's formula
RCC	Renal cell carcinoma
R Value	ALT/ALP using multiples of the ULN for both values
SAE	Serious Adverse Event
SAP	The Statistical Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
SBP	Systolic blood pressure
SC	Steering Committee
SD	Stable disease
STS	Soft Tissue Sarcoma
TBIL	Total bilirubin
TKI	Tyrosine kinase inhibitor
[redacted]	[redacted]
ULN	Upper limit of normal
UPC	Urine Protein to Creatinine Ratio
US	United States
VEGFR	Vascular endothelial growth factor receptor

[redacted]

Glossary of terms

Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

[redacted]

Amendment 2 (14-Sep-2020)

Amendment rationale

As of amendment date, 8 patients remain on study treatment in two countries (Chile-2 sites and France-1 site).

Novartis procedures for collecting follow up information on pregnancies have been revised to harmonize follow-up timelines across product platforms. The follow up period for collecting information after a live birth has been extended from 3 months to 12 months. The ICFs for pregnant participant and pregnant partner are updated accordingly.

A typographical error is also corrected.

The changes reflected in this amendment are listed below.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Section 8.4 Pregnancies: Extended the duration of the pregnancy follow up period from 3 months to up to 12 months post-birth.
- Section 7.2.1, Table 7-3 Imaging Assessment Collection Plan: Typographical error corrected. During efficacy follow up, scans are mandated every 8 weeks (± 7 *days*), not every 8 weeks (± 7 weeks).

[redacted]

Amendment 1 (9-Feb-2018)

Amendment rationale

As of 30-Jan-2018:

- 2 patients in 2 countries have been enrolled;
- 1 patient has discontinued treatment

Since the original protocol was finalized in April 2017, the RCC treatment landscape has evolved. There are several ongoing trials evaluating immune checkpoint inhibitor combinations (IO-IO) or IO-Tyrosine Kinase Inhibitor (TKI) combinations as first line therapy, and IO is expected to become the standard of care in first line therapy. Data collected from the use of pazopanib in the 2nd line setting post-immune checkpoint inhibitor therapy are now more relevant. Furthermore, the availability of other agents including cabozantinib may present potential challenges to recruitment. Therefore, the sample size is being reduced from 140 to approximately 100 patients to obtain relevant data in a timely manner. The reduced sample size will provide 2.78 months precision with a 95% CI of (4.77, 7.55) for an estimate median PFS of 6 months.

Therapeutic lines of pazopanib – whether in the 2nd or 3rd line setting - will be tracked at screening using Integrative Response Technology (IRT) with an enrollment cap to ensure that approximately 40% patients enroll with pazopanib administered as 2nd line treatment. Descriptive summary statistics for the primary efficacy and safety data will be provided by pazopanib line of treatment in addition to other relevant subgroups.

As there is limited evidence to support re-challenge with pazopanib after prior 1st line pazopanib followed by IO, patients with previous exposure to pazopanib will be excluded from study participation.

To allow for early monitoring of blood pressure soon after starting treatment with pazopanib, vital signs measurement has been added on Cycle 1 Day 8. The frequency of cardiac imaging has been reduced to every 5-6 cycles unless otherwise indicated. These changes are consistent with the Investigator's Brochure.

The major changes reflected in this amendment are listed below.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Section 1.2.1.2: Updated number of patients exposed to pazopanib per Investigator's Brochure v16.
- Section 2.2: Added text supporting reduction in sample size and addition of enrollment cap for patients receiving pazopanib as 3rd line therapy. Added precision for estimated median PFS for 2nd and 3rd line subgroups.
- Section 4.1: Added that therapeutic lines of pazopanib will be tracked at screening with an enrollment cap to ensure that approximately 40 patients receive pazopanib administered as 2nd line treatment.

[redacted]

- Section 5.1: Changed sample size from 140 to approximately 100 patients, with approximately 40 patients receiving 2nd line pazopanib therapy.
- Section 5.2: Clarified inclusion criterion #5 to allow enrollment of patients with prior mTOR inhibitor treatment. Added requirement for serum calcium to be within normal limits at screening.
- Section 5.3: Added exclusion criterion to disallow enrollment of patients previously treated with pazopanib.
- Section 5.3: Updated exclusion criterion #2 to allow enrollment of patients who have previously-treated CNS metastases that meet three additional criteria.
- Table 6-2: Changed units for febrile neutropenia (ANC < 1000/mm3) for consistency.
- Table 6-2, 7-2: If QTcF interval is ≥ 500 msec, added that monitoring in a hospital is required until a cardiologist's evaluation has been obtained.
- Section 6.4.2: Added details of enrollment cap implementation via IRT.
- Table 7-1: Added Cycle 1 Day 8 assessment of vital signs. Reduced frequency of cardiac imaging to screening, Cycles 5, 11, 16 and every 6th cycle thereafter until end of treatment)
- Table 7-1, Section 7.1.1.3: Clarified that screening quality of life questionnaires can be obtained from Day -7 until Cycle 1 Day 1 predose.
- Section 7.2.2.5.8: Clarified that at-home urine pregnancy test kits will be supplied to patients by each site, not by central lab (Covance)
- Section 7.2.5: Clarified that both screening quality of life questionnaires must be completed during the screening phase within 7 days before the first dose of study medication (pazopanib) only after patient eligibility is confirmed, or on Cycle 1 Day 1 predose.
- Section 7.2.2.6.2: To support reduced frequency of cardiac imaging, added that patients should be closely monitored for signs and symptoms of congestive heart failure. In particular, patients at risk of cardiac dysfunction or with prior anthracycline exposure may warrant more frequent monitoring.
- Table 7.5: Added footnote that interference with Total T3 and Free T4 assays may be observed in patient taking high doses of biotin. It is recommended that biotin supplements be stopped for 3 days prior to sampling.
- Table 7.5: Updated footnote regarding local lab tests for hepatoxicity follow-up. Added "where locally available".
- Table 7-7: Updated cardiac imaging timepoints (as reflected in Table 7-1 schedule of assessments)
- Sections 10, 10.4.4: Defined subgroups for primary efficacy and selected safety analyses
- Section 10.5.3.2, 10.5.3.3: Added that adverse events and laboratory abnormalities will also be tabulated by line of therapy subgroup (2nd/3rd), age category and MSKCC and IMDC risk groups.
- Section 10.8: Updated sample size and estimated 95% CI for median PFS.

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Title	A prospective international multicenter phase II study to evaluate the efficacy, safety and quality of life of pazopanib in patients with advanced and/or metastatic renal cell carcinoma after previous therapy with checkpoint inhibitor treatment
Brief title	Study of efficacy and safety of pazopanib in patients with advanced and/or metastatic renal cell carcinoma after prior checkpoint inhibitor treatment
Sponsor and Clinical Phase	Novartis Pharma AG II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Immunotherapy has played an important role in the treatment of renal cell carcinoma (RCC). For over 2 decades, cytokine therapy with interleukin-2 (IL-2) or interferon alpha was the mainstay 1st therapy for patients with metastatic RCC but eventually was replaced by VEGF targeted agents. Advances in our understanding of the immune checkpoints have led to the development of novel approaches for cancer therapy, including anti-CTLA-4, anti-PD-1 and anti-PD-1L antibodies. The RCC landscape is evolving rapidly with multiple treatment options in second line. Currently, there are several ongoing clinical trials with immune checkpoint inhibitors in different malignancies including RCC; however combinations of dual immune checkpoint inhibitors, and combinations of vascular endothelial growth factor receptor (VEGF)-directed agents with immune checkpoint inhibitors, may not produce durable responses in all patients and many patients will eventually relapse (Larkin 2016, Atkins 2016, Hammers 2016). VEGF-directed therapies will, therefore, continue to play a major role in the management of patients with mRCC (metastatic RCC), even as novel immune therapies gain FDA approval for mRCC. No prospective data are available on the efficacy of pazopanib after previous treatment with an immune checkpoint inhibitor. Additionally, the majority of clinical trials conducted in first line RCC with checkpoint inhibitors use a control arm treatment with sunitinib. Interim analyses of some first line trials were reported in 2017 and are ongoing in 2018 with potential to change first line standard of care (NCT02853331, NCT02231749, NCT02684006, and NCT02420821). The goal of this phase II trial is to evaluate the efficacy, tolerability, safety and quality of life of patients with mRCC treated with pazopanib following treatment with immune checkpoint inhibitors.
Primary Objective(s)	**Primary:** To assess the progression-free survival (PFS) based on local investigator assessment using RECIST 1.1.
Secondary Objectives	• To assess overall response rate (ORR) and clinical benefit rate (CBR) based on local investigator assessment • To assess overall survival (OS) • To assess duration of response (DOR) in patients with confirmed complete response (CR) or partial response (PR) • To evaluate safety and tolerability • To assess quality of life

[redacted]

Study design	An international, multicenter, single arm Phase II trial to determine the efficacy, safety and quality of life of pazopanib treatment after previous therapy with immune checkpoint treatment Approximately 100 patients will be enrolled. Since data collected from the use of pazopanib in the 2nd line setting post-IO therapy will be the most relevant, therapeutic lines of pazopanib – whether in the 2nd or 3rd line setting - will be tracked at screening using Integrative Response Technology (IRT) with an enrollment cap to ensure that approximately 40 patients receive pazopanib as 2nd line treatment. Patients will receive treatment with standard dose pazopanib until disease progression, unacceptable toxicity, pregnancy, death, discontinuation from the study treatment for any other reason or until 2 years after LPFV, whichever event comes first. All patients who discontinue treatment will be followed for survival for 2 years after LPFV. Patients who discontinue treatment without documented disease progression will be followed for efficacy for 1 year after LPFV.
Population	The study will include approximately 100 adults with advanced and/or metastatic renal cell carcinoma who have been previously treated with immune checkpoint therapy.
Key inclusion criteria	• Patient is ≥ 18 years old at the time of informed consent. • Patient has histologically confirmed locally recurrent or metastatic predominantly clear cell renal cell carcinoma. • Patient must have measurable disease based on RECIST 1.1 criteria • Patient must have received prior systemic therapy with an immune checkpoint inhibitor (monotherapy or combination) as 1st or 2nd line RCC treatment. Note: patients with prior TKI treatment or mTOR inhibitor as monotherapy or in combination with immune checkpoint inhibitor are allowed; however, treatment with immune checkpoint inhibitor (monotherapy or in combination) must have been the last treatment prior to study entry. • Last dose of immune checkpoint inhibitor therapy must have been received 4 or more weeks before start of study treatment • Patient must have a Karnofsky performance status ≥70%.
Key exclusion criteria	• Renal cell carcinoma without any clear (conventional) cell component • Presence of Central Nervous System metastases (patients with pretreated metastases are eligible under certain conditions) • Prior treatment with bevacizumab that was not given in combination with immune checkpoint inhibitor therapy. • Prior treatment with more than 2 lines of therapy (combination treatments are considered 1 line of therapy) • Prior treatment with pazopanib • Patient has not recovered from toxicity from prior immune checkpoint inhibitor therapy. Recovery is defined as ≤ NCI-CTCAE Grade 1, except for liver function test (LFT) levels which must be <Grade 1. • Disease recurrence less than 6 months from the last dose of prior neoadjuvant or adjuvant therapy (including VEGF-R TKI) • Patients receiving prohibited concomitant medications that cannot be discontinued or replaced by safe alternative medication at least 5 half-lives of the concomitant medication or 7 days, whichever is longer, prior to the start of pazopanib treatment. • Administration of any investigational drug within 4 weeks prior to the first dose of study treatment
Investigational and reference therapy	Pazopanib 800 mg QD

[redacted]

Efficacy assessments	• CT/ MRI every 8 weeks for the first 12 months, then every 12 weeks thereafter. • Brain CT or MRI as clinically indicated. • Whole body scan, mandatory at screening then as clinically indicated • Bone x-ray, CT or MRI (if bone lesion at screening) every 8 weeks for the first 12 months and then every 12 weeks thereafter. • CT/ MRI for any disease outside of the chest, abdomen, pelvis (if lesion identified at baseline) every 8 weeks for the first 12 months and then every 12 weeks thereafter. • Efficacy follow up every 8 weeks, only for patients who discontinue study treatment without documented disease progression • Survival status every 12 weeks regardless of treatment discontinuation reason, except withdrawal of consent
Safety assessments	• Physical examinations • Karnofsky performance status • Weight and vital signs • 12 lead electrocardiograms (ECGs) • Cardiac imaging • Laboratory assessments including hematology, chemistry, coagulation, thyroid, urinalysis and pregnancy tests
Other assessments	[redacted] The EuroQoL 5-level instrument (EQ-5D-5L, Version 4.0) and FKSI-DRS will be used to explore patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms and treatment-related side effects.
Data analysis	The primary efficacy and safety analyses will be conducted after all patients have completed 6 cycles of study treatment or have discontinued early. No formal hypothesis will be tested in the study. An estimation of the median PFS with 95% confidence intervals will be provided in the full analysis set (FAS) population. The Kaplan-Meier estimate of the PFS survival function will be estimated and displayed. The resulting median PFS time will be given with 95% confidence intervals, and 25th and 75th percentiles will be reported. PFS probability at selected time-points (e.g., 3, 6 and 12 months) will also be estimated.
Key words	Advanced renal cell carcinoma, metastatic renal cell carcinoma, Phase II, pazopanib, checkpoint inhibitor therapy

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

RCC arises in the cells of the renal tubules and is the most common (90-95%) of several clinically and epidemiologically distinct types of renal carcinoma (Gupta 2008). The main histologic tumor types of RCC include clear cell (non-papillary), papillary (chromophilic), chromophobe, oncocytic, collecting duct and unclassified (Cohen 2005).

Kidney cancer accounts for 5% and 3% of all adult malignancies in men and women respectively, thus representing the 6th most common cancer in men and the 10th most common cancer in women (Siegel 2017). However, available statistics include not only renal parenchymal tumors (adenocarcinoma cell type [RCC]), but also renal pelvic tumors (renal transitional cell type). Renal cell carcinoma (RCC) accounts for ~90% of all kidney cancers (Chow 2010).

After over two decades of increasing rates, RCC incidence trends worldwide have shown signs of plateauing or decreasing in recent years. Furthermore, kidney cancer mortality rates overall have leveled. These patterns are consistent with reports of incidental diagnosis and a downward shift of tumor stage and size due to early detection. Aside from well-known risk factors for RCC, such as cigarette smoking, obesity and hypertension, evidence is accumulating to suggest an association between the development of RCC and other factors, such as physical activity, alcohol consumption and occupational exposure to trichloroethylene and parity in women (Chow 2010). RCC also appears to be more common in patients with end stage renal failure or acquired renal cystic disease, and in patients on dialysis, those who have had kidney transplantation, or those with tuberous sclerosis syndrome. Approximately 2%–3% of all RCCs are hereditary and several autosomal dominant syndromes are described, each with a distinct genetic basis and phenotype, the most common one being Von Hippel Lindau (VHL) disease (Escudier 2016).

Three treatments have demonstrated efficacy in pivotal phase III trials first-line treatment of patients with mRCC and good or intermediate prognosis: bevacizumab (combined with interferon) (Escudier 2007), sunitinib (Motzer 2007), and pazopanib (Sternberg 2010). All three drugs have been registered based on improvement of progression-free survival (PFS) over either interferon or placebo. More recently, pazopanib has been shown to be non-inferior to sunitinib in a large phase III trial (COMPARZ- Motzer 2013). The primary endpoint was PFS; secondary endpoints include overall survival, duration of response, quality of life, medical resource utilization and safety assessments. The study demonstrated non-inferiority of pazopanib for PFS in the intention to treat population and pazopanib statistically favoured quality of life in 11 of the 14 domains measured (Motzer 2013). Efficacy of both sunitinib and pazopanib has been confirmed by real-world evidence studies. These two tyrosine kinase inhibitors (TKIs) are currently the most commonly used treatments (Escudier 2016). Temsirolimus is currently the only drug tested in a phase III study, demonstrating evidence of activity as a first line treatment in patient with poor prognosis. The pivotal trial demonstrated improvement of OS compared with interferon or the combination of temsirolimus and interferon (Hudes 2007).

[redacted]

After first-line treatment with VEGF-targeted therapy, both axitinib and everolimus are active (Rini 2011) (Motzer 2008). Both drugs have shown significantly improved PFS over sorafenib (axitinib) or placebo (everolimus). However, according to 2016 ESMO Clinical Practice Guidelines, second-line treatment has recently been dramatically modified by the report of two large trials showing improvement in OS with nivolumab [an anti-programmed death 1 (PD-1) inhibitor] (Motzer 2015) and cabozantinib over everolimus (Choueiri 2015). Both trials showed significant improvement in OS and response rate, while only PFS was improved in the cabozantinib trial. In both trials, patients could be treated after either one or two TKIs. In countries where these drugs are not available: either everolimus or axitinib can be used. Of note, the combination of lenvatinib and everolimus has recently been approved by the FDA (Food and Drug Administration) based on a randomized study of 150 patients, showing PFS and OS benefit over everolimus (Motzer 2015). Recently in Europe, the CHMP (Committee for Medicinal Products for Human Use) gave a positive opinion for this combination (Escudier 2016).

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of pazopanib (Votrient®)

Pazopanib is a multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and -β, fibroblast growth factor receptor (FGFR)-1 and -3, cytokine receptor (Kit), interleukin-2 receptor-inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck) and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). Further information on pazopanib may be found in the prescribing information or the pazopanib Investigators Brochure (IB).

Votrient was first approved on 19 Oct 2009 in the USA for the treatment of advanced RCC at a dose of 800 mg daily. The European Commission granted conditional approval for the marketing authorization application on 14 Jun 2010 and granted full approval on 14 Jun 2013. The therapeutic indication for Votrient has been expanded to include treatment for advanced Soft Tissue Sarcoma (STS) with approval in the USA on 26 Apr 2012, European Union on 03 Aug 2012 and Japan on 28 Sep 2012. Votrient is currently approved in more than 101 countries including the following: Australia, Canada, Switzerland, Brazil, Russia, and India for either or both of these indications. [redacted]

Votrient is indicated for the following: treatment of advanced renal cell carcinoma and for the treatment of advanced soft tissue sarcoma in patients who have received prior chemotherapy (Limitation of Use: The efficacy of Votrient for the treatment of patients with adipocytic soft tissue sarcoma or gastrointestinal stromal tumors has not been demonstrated). In the US, Votrient is registered for treatment of advanced and/or metastatic RCC and the treatment of adult patients with selective subtypes of advanced Soft Tissue Sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months

[redacted]

after (neo) adjuvant therapy (the Phase III trial population excluded patients with gastrointestinal stromal tumor (GIST) or adipocytic STS in the EU).

1.2.1.1 Non-clinical experience

A range of nonclinical pharmacology, pharmacokinetic and toxicology studies have been performed with pazopanib. It is described in the latest Investigator's Brochure.

1.2.1.2 Clinical experience

Cumulatively, as of 09 September 2017, approximately 8724 patients and healthy volunteers were enrolled and treated in pazopanib clinical studies, of whom 5897 received pazopanib as monotherapy or in combination with other chemotherapeutic agents. Data collected to date show that pazopanib administration at 800 mg daily is associated with a reasonable safety profile and encouraging efficacy in various oncology settings.

1.2.1.2.1 Efficacy of pazopanib in advanced/metastatic RCC

In study VEG105192 (a randomized, double-blind, placebo-controlled Phase III study of pazopanib monotherapy in subjects with advanced RCC), the primary analysis of the primary endpoint, progression-free survival (PFS), revealed a highly statistically significant improvement in PFS in the pazopanib-treated subjects compared to placebo-treated subjects (hazard ratio [HR] 0.46, 95% CI 0.34 to 0.62, $p<0.0000001$). The median PFS in the pazopanib arm was more than double that in the placebo arm: 9.2 months (95% CI, 7.4, 12.9) versus 4.2 months (95% CI, 2.8, 4.2), respectively. The response rate was significantly higher for the pazopanib arm compared with the placebo arm by IRC assessment (30% vs. 3%, $p<0.001$). In the pazopanib arm, the median duration of response was 58.7 weeks (95% CI, 52.1 to 68.1 weeks) and the median time to response was 11.9 weeks (95% CI, 9.4 to 12.3 weeks) by independent radiologic review assessment (Sternberg 2010). The median OS at final analysis was 22.9 months in the pazopanib arm and 20.5 months in the placebo arm. The final OS was not statistically different between the pazopanib arm and the placebo arm in (HR = 0.91, stratified log-rank p-value, 0.224) (Sternberg 2013).

In study VEG108844, pazopanib demonstrated to be non- inferior to sunitinib with respect to IRC-assessed PFS (HR 1.047; 95% CI 0.8982, 1.2195). The median PFS was 8.4 months (95% CI, 8.3, 10.9) for pazopanib and 9.5 months (95% CI, 8.3, 11.1) for sunitinib. OS was similar between the treatment arms (HR 0.908; 95% CI 0.762, 1.082, $p=0.275$). The median OS was 28.4 months (95% CI: 26.2, 35.6) in pazopanib and 29.3 months (95% CI: 25.3, 32.5) in the sunitinib arm. IRC-assessed overall response rate was greater in the pazopanib arm (31%; 95% CI 26.9, 34.5) than the sunitinib arm (25%; 95% CI 21.1, 28.4) and the difference (6%) was statistically significant ($p=0.032$). Overall, the results for PFS, OS, and ORR support similar efficacy for pazopanib and sunitinib (Motzer 2013). At the time of the final OS analysis (data cut-off 30 September 2013), again OS was similar between the treatment arms with a hazard ratio of 0.915 (95% CI: 0.786, 1.065, $p=0.245$). Median OS was 28.3 months (95% CI: 26.0, 35.5) in the pazopanib arm and 29.1 months (95% CI: 25.4, 33.1) in the sunitinib arm (Motzer 2013). In study VEG107769 the response rate was 37.5%, the median PFS was 9.2 months, and the median OS was 23.5 months. The data cut-off for this analysis was 15 March 2010 by that time 64% of subjects had died, compared with 30% at the time of the primary analysis.

[redacted]

1.2.1.2.2 Safety of pazopanib in advanced/metastatic RCC

In VEG105192, the median time on treatment was approximately twice that on placebo (7.4 months versus 3.8 months) (Sternberg 2010). The overall frequency of adverse events (AEs) reported during the study was higher in the pazopanib arm (93%) compared with placebo (74%). Most common AEs reported in >20% subjects in the pazopanib arm, regardless of grade and causality (as of 29 Dec 2014 – end of study), were diarrhea (52%), hypertension (40%), hair color changes (38%), nausea (26%), decreased appetite (24%), and vomiting (21%). These AEs were all reported at a higher incidence in the pazopanib arm than in the placebo arm. Most of these events were Grade 1 or 2 using the NCI Common Toxicity Criteria for Adverse Events (NCI CTCAE) Version 3.0. More Grade 3 AEs were reported in the pazopanib arm (33%) compared with the placebo arm (14%). The frequency of Grade 4 AE and Grade 5 events was similar between the pazopanib and placebo arms: Grade 4 in 7% and 6%, respectively; Grade 5 in 4% and 3%, respectively. The most common Grade 3/4 events in the pazopanib arm were ALT increased, hypertension, AST increased, diarrhea and asthenia/fatigue.

Based on the analysis of the safety data integrated across the 3 RCC studies VEG102616 (a Phase II study of pazopanib monotherapy in subjects with advanced RCC), VEG105192, and VEG107769 (a single arm Phase III extension study of pazopanib monotherapy in subjects with advanced RCC) as of 09 January 2009 (N=593), the most common AEs and serious adverse events (SAEs) were similar to those observed in the pazopanib arm of VEG105192.

Study VEG102616 (completed 10 September 2013) confirms the safety profile of pazopanib and no new safety signals were observed. The most common AEs were diarrhea (66%), fatigue (48%), hair color changes (44%), hypertension (44%) and nausea (44%), which is consistent with the primary analysis (safety data cut-off date, 24 March 2008).

Study VEG107769 was completed (20 December 2012), and again no new safety signals for pazopanib were observed. The median duration of exposure to pazopanib was 9.7 months (range: 0 months to 56 months). The most common AEs (>20% subjects) were hypertension (45%), diarrhea (45%), hair color changes (44%), decreased appetite (30%), and nausea (25%). Thirty-seven percent of subjects experienced an AE of maximum grade 3 severity or higher.

Study VEG108844 is a randomized, open-label, parallel group Phase III non-inferiority study to evaluate the efficacy and safety of pazopanib compared with sunitinib in subjects with advanced RCC who had not received prior systemic therapy for advanced or metastatic RCC. Approximately 876 eligible subjects (approximately 438 per treatment arm) were planned to be enrolled over the course of the study. However, due to higher than expected withdrawal rates and discordance rates between Independent Review Committee (IRC) and investigator assessments of progression, the protocol was amended to increase the number of subjects to approximately 1100 total by including all subjects enrolled in VEG108844 and VEG113078 (a substudy of VEG108844). VEG113078 was conducted in China, Korea, and Taiwan; enrolled the same subject population as VEG108844; and is almost identical in study design and conduct to allow integration of efficacy and safety data.

A total of 1102 subjects were included in the safety population (pazopanib 554 subjects; sunitinib 548 subjects). At the time of the OS analysis (data cut-off 30 September 2013) the median time on treatment was 8.1 months for pazopanib and 7.6 months for sunitinib. The overall frequency of AEs reported during the study was similar for each treatment group; 552

[redacted]

subjects (>99%) had AEs in the pazopanib arm and 544 subjects (>99%) had AEs in the sunitinib arm. However, differential safety profiles were observed between the treatment arms, with a statistically significant difference in frequencies (unadjusted for multiplicity) for several AEs. The most common AEs (>35% in either treatment arm) were diarrhea (63% in pazopanib arm, 57% in sunitinib arm), fatigue (55% in pazopanib arm, 63% in sunitinib arm), hypertension (47% in pazopanib arm, 41% in sunitinib arm), nausea (45% in pazopanib arm, 46% in sunitinib arm), decreased appetite (38% in pazopanib arm, 37% in sunitinib arm), dysgeusia (26% in pazopanib arm, 36% in sunitinib arm), and palmar-plantar erythrodysesthesia (PPE) syndrome (or hand-foot syndrome [HFS]) (30% in pazopanib arm, 50% in sunitinib arm).

Of these AEs, fatigue, HFS, and dysgeusia occurred more frequently in the sunitinib arm compared with the pazopanib arm based on 95% confidence interval (CI; unadjusted for multiplicity) for relative risk excluding 1. The proportion of subjects with diarrhea and hypertension was higher in pazopanib compared with sunitinib. Three additional subjects in the pazopanib arm had an AE of diarrhea since the cut-off date for the primary analysis. As a result, the 95% CI for relative risk for this event now excludes 1, whereas previously it did not. The proportion of subjects with maximum Grade 3 and 4 AEs was similar between the treatment arms, with no difference in the relative risk. Grade 3 AEs of increased ALT, increased aspartate aminotransferase (AST), and headache occurred more frequently in the pazopanib arm compared with the sunitinib arm. Grade 3 AEs of fatigue, decreased appetite, HFS, neutropenia, mucosal inflammation, thrombocytopenia, leukopenia, decreased platelet count, anemia, and decreased neutrophil count occurred more frequently in the sunitinib arm compared with the pazopanib arm. Grade 5 AEs were reported in 13 (2%) subjects in the pazopanib arm and 19 (3%) subjects in the sunitinib arm. Since the data cut-off for the primary analysis CSR, one additional subject in the pazopanib arm had a fatal SAE of lung infection

1.2.1.2.3 Summary of pharmacokinetic and pharmacodynamic data

Results of pharmacokinetic and pharmacodynamic analyses demonstrate that pazopanib is absorbed after oral administration; a plateau is reached in steady-state systemic exposure at a dose of 800 mg daily; therefore, increases in doses above 800 mg, up to the highest dose evaluated (2000 mg), in the fasted state do not result in a consistent increase in systemic exposure. Oral absorption is significantly enhanced when pazopanib is dosed with food; therefore, it is recommended to administer pazopanib on an empty stomach.

Consistent with VEGF receptor inhibition, a monotherapy dose of 800 mg once daily, resulted in increased blood pressure, increases in VEGF, and decreases in soluble VEGFR-2. Concentration-effect relationships were observed between pazopanib trough plasma concentrations and an increase in blood pressure (Study VEG10003), as well as in the percent change from baseline in soluble VEGFR-2 (Study VEG102616).

1.2.1.2.4 Drug-drug interactions

Pazopanib is metabolized primarily by CYP3A4 and systemic exposure to pazopanib is altered by inhibitors and inducers of this enzyme. Co-administration of pazopanib with strong CYP3A4 inhibitors or inducers is predicted to increase or decrease, respectively, the systemic exposure to pazopanib. The concomitant use of strong CYP3A4 inhibitors or inducers should be avoided.

[redacted]

If co-administration with a strong CYP3A4 inhibitor cannot be avoided, pazopanib dose should be reduced (see Appendix 1).

There were no clinically meaningful changes in QTc interval following pazopanib in a dedicated QT Holter study.

2 Rationale

2.1 Study rationale and purpose

Immunotherapy has played an important role in the treatment of RCC. For over 2 decades, cytokine therapy with interleukin-2 (IL-2) or interferon alpha was the mainstay first-line therapy for patients with metastatic RCC but eventually was replaced by VEGF targeted agents. Advances in our understanding of the immune checkpoints have led to the development of novel approaches for cancer therapy, including anti-CTLA-4, anti-PD-1 and anti-PD-1L antibodies. The RCC landscape is evolving rapidly with multiple treatment options in second line. Nivolumab was recently approved in second line following the results of the Checkmate-025 study (Motzer 2015).

Currently, there are several ongoing clinical trials with immune checkpoint inhibitors in different malignancies including RCC; however combinations of dual immune checkpoint inhibitors, and combinations of immune checkpoint inhibitors with VEGF-directed agents, may not produce durable responses in all patients and many patients will eventually relapse (Larkin 2016, Atkins 2016, Hammers 2016). VEGF-directed therapies will, therefore, continue to play a major role in the management of patients with mRCC, even as novel immune therapies garner FDA approval for mRCC. No prospective data are available on the efficacy of pazopanib after previous treatment with an immune checkpoint inhibitor. Additionally, the majority of clinical trials conducted in first line RCC with checkpoint inhibitors use a control arm treatment with sunitinib. Interim analyses of some first line trials were reported in 2017 and others will be available in 2018 with potential to change first line standard of care (NCT02853331, NCT02231749, NCT02684006, and NCT02420821).

The goal of this phase II trial is to evaluate the efficacy, tolerability, safety and quality of life of patients with mRCC treated with pazopanib following prior treatment with immune checkpoint inhibitors.

2.2 Rationale for the study design

In a retrospective study, Nadal et al (2016) reported an ORR of 27% in mRCC patients treated with VEGFR-TKI therapy after any PD-1 combination, with median PFS (mPFS) of 6.9 months (95% CI: 3.7 to 10.1). Albiges et al (2015) reported a median time to treatment failure of 6.9 months and 5.7 months in patients who received VEGFR-TKI and mTOR inhibitors after checkpoint inhibitor, respectively.

The efficacy and safety of anti-VEGF TKI after immune checkpoint inhibitor therapy need to be studied in a prospective trial. Since the aim of the study is to evaluate efficacy and safety of pazopanib in patients previously treated with checkpoint inhibitors, and currently there is no approved standard of care treatment for this specific patient population, no control arm has been included in the trial design. This trial is neither designed nor intended to compare efficacy and

[redacted]

safety to a standard of care, but to address the use of TKI therapy post immune checkpoint inhibitor. Results will be evaluated in light of previously reported data in similar populations in the context of the evolving RCC treatment landscape.

There are several ongoing trials evaluating immune checkpoint inhibitor combinations (IO-IO) or IO-Tyrosine Kinase Inhibitor (TKI) combinations as 1st line therapy, and IO is expected to become the standard of care in 1st line therapy. Data collected from the use of pazopanib in the 2nd line setting post-IO therapy will be more relevant, but these patients may also be more difficult to recruit for this study based on local treatment practices. Given the very specific patient population, a sample size of 100 patients is based on the estimated feasibility of enrolling a sufficient number of relevant patients in a timely manner, and not based on any statistical power considerations. This sample size will provide 2.78 months precision with a 95% CI of (4.77, 7.55) for an estimate median PFS of 6 months (overall). For 2nd line and 3rd line patients, the precision with a 95% CI for estimated PFS is provided in Section 10.8.

Therapeutic lines of pazopanib – whether in the 2nd- or 3rd-line setting - will be tracked at screening using Integrative Response Technology (IRT) with an enrollment cap to ensure that approximately 40 patients enroll with pazopanib administered as 2nd-line treatment.

2.3 Rationale for dose and regimen selection

Votrient (pazopanib) is approved for the treatment of patients with advanced renal cell carcinoma (RCC). The recommended and approved starting dose is 800 mg orally once daily which is the starting dose that will be used in this study.

2.4 Rationale for choice of combination drugs

Not applicable

2.5 Rationale for choice of comparators drugs

Not applicable

2.6 Risks and benefits

Pazopanib 800 mg daily is considered to have a positive benefit-risk profile for patients with advanced renal cell carcinoma; the benefits of therapy with pazopanib outweigh any potential risks. Per the Investigator's Brochure, the last review of all available pazopanib data does not change the Benefit/Risk profile which remains positive and supports the use of pazopanib in this patient population.

Appropriate eligibility criteria as well as specific dose modification and stopping rules, are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.2. The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as, close clinical monitoring. There may be unforeseen risks with pazopanib. Refer to the latest Investigator's Brochure.

[redacted]

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
To assess the progression-free survival (PFS) based on local investigator assessment	PFS based on local investigator assessment using RECIST v1.1 defined as the time from the first administration of study treatment until the first documented progressive disease (PD) or death due to any cause.	
Secondary		Refer to Section 10.5.2.
To assess overall response rate (ORR) and clinical benefit rate (CBR) based on local investigator assessment	ORR defined as the proportion of patients with best overall response of confirmed complete response (CR) or partial response (PR) based on local investigator's assessment according to RECIST v1.1 CBR defined as the proportion of patients with a best overall response of CR or PR or an overall lesion response of stable disease (SD), or Non-CR/Non-PD lasting ≥ 24 weeks based on local investigator's assessment according to RECIST v1.1.	
To assess overall survival (OS)	Overall survival (OS) defined as the time from the first administration of study treatment until death due to any cause	
To assess duration of response (DOR) in patients with CR or PR	DOR defined as the time from the date of first documented response (confirmed CR or PR) to the date of tumor progression	
To evaluate the safety and tolerability	Type, frequency and severity of AEs per NCI-CTCAE v4.03. Type, frequency and severity of laboratory toxicities per NCI-CTCAE v4.03	Refer to Section 10.5.3.
To assess quality of life	Quality of life as assessed by the EuroQoL EQ-5D-5L and FKSI-DRS health questionnaire	Refer to Section 10.5.5.

[redacted]

[redacted]

4 Study design

4.1 Description of study design

This is a multi-center, open-label, single-arm phase II study to determine the efficacy, tolerability, safety and quality of life of treatment with pazopanib in patients with advanced and/or metastatic renal cell carcinoma following prior treatment with immune checkpoint inhibitors.

Therapeutic lines of pazopanib – whether in the 2nd- or 3rd-line setting - will be tracked at screening using Integrative Response Technology (IRT). Enrollment of 3rd line patients may be restricted to ensure approximately 40 patients receive pazopanib as 2nd line therapy.

Patients will receive standard dose of pazopanib daily until disease progression, unacceptable toxicity, death, pregnancy, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient, lost to follow-up, end of study or study is terminated by the sponsor, whichever comes first. Dose modifications will be allowed for patients who do not tolerate the standard starting dose of 800 mg daily. Patients will be followed for survival (except if consent is withdrawn or patient is lost to follow-up).

The cut-off date for the primary analysis will occur after all patients have received a minimum of 6 cycles of study treatment or have discontinued study treatment early. The primary analysis data will be summarized in the primary clinical study report (CSR).

4.1.1 Screening phase (Day -28 to Day -1 or Day -7 to Day -1 for certain procedures)

Patients must provide a signed Informed Consent Form (ICF) prior to any study specific evaluations including screening. Eligibility will be determined according to the inclusion/exclusion criteria as described in Section 5. A list of procedures to be performed at the time of screening is summarized in Table 7-1. Patients must meet all eligibility criteria to enter the study.

4.1.2 Treatment phase (Cycle 1 Day 1 to EOT)

Patient eligibility will be checked once all screening procedures are completed. The eligibility check will be performed through the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

Efficacy assessments will be conducted every 8 weeks during the first 12 months and every 12 weeks thereafter. Safety assessments and PRO questionnaires will be performed according to Table 7-1. Please refer to Table 7-1 and Section 7 for the complete assessment schedule and details.

4.1.3 Safety follow-up (EOT + 30 days)

After discontinuation of study treatment, all patients will be followed for safety for 30 days except in case of death, loss to follow up or withdrawal of consent. For details, please refer to Section 7.1.5.1.

[redacted]

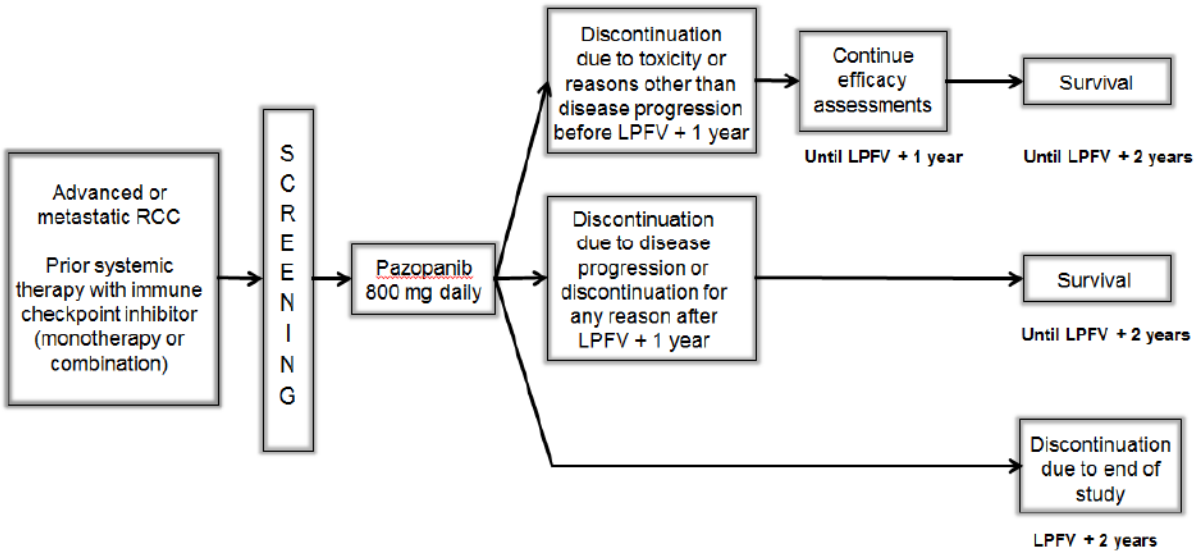
4.1.4 Efficacy follow-up (EOT until progression or 1 year from LPFV)

Patients who discontinue study treatment without disease progression by RECIST 1.1 before LPFV + 1 year will continue to be followed for efficacy every 8 weeks until disease progression, death, pregnancy, withdrawal of consent, loss to follow-up, patient/guardian decision, study terminated by sponsor or until LPFV + 1 year, whichever comes first. For further details, please refer to Table 7-1 and Section 7.1.5.2.

4.1.4.1 Survival follow-up (EOT + 2 years from LPFV)

Patients will be followed for survival every 12 weeks until LPFV + 2 years. Patients, who discontinue study treatment without disease progression and enter the efficacy follow-up, will not begin survival follow-up until after the efficacy follow-up period. For patients who discontinue study treatment due to disease progression by RECIST 1.1 at any time or for any reason after LPFV + 1 year, survival follow-up will begin following end of treatment. Survival information can be obtained by clinical visits or telephone calls (Section 7.1.6) until death, lost to follow up or the patient withdraws consent for survival follow-up. For further details, please refer to Table 7-1 and Section 7.1.5.3.

Figure 4-1 Study design



4.2 Timing of interim analyses and design adaptations

No formal interim analysis is planned.

4.3 Definition of end of study

The end of study will occur 2 years after the last patient is enrolled, or when all patients have died or discontinued from the study and are no longer being followed for survival, whichever occurs first. All available data from all patients will be analyzed and summarized in a final CSR.

[redacted]

Patients who are still deriving benefit from the treatment at the end of the study, in the opinion of the investigator, should be switched to a local prescription in case Votrient is commercially available and reimbursed in that country. For countries in which Votrient is not reimbursed, nor commercially available or for patients who cannot afford treatment, Novartis will make every effort to continue to provide treatment with pazopanib through another program per local regulations.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a patient who has discontinued or been withdrawn from treatment. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The study will include adult patients with advanced and/or metastatic RCC immediately after previous therapy with immune checkpoint inhibitor, either as single agent or in combination with other therapies (TKIs or other immune checkpoint inhibitors) in the first or second line. Eligible patients may have also had prior single agent TKI treatment in 1st line setting; however, the last therapy before enrollment in the study, must be a checkpoint inhibitor (single agent or in combination) either in 1st or 2nd line setting.

A total of approximately 100 patients are planned to enroll in this study, with approximately 40 of those patients receiving pazopanib as 2nd-line therapy. Patients enrolled in this study are not permitted to participate in any other investigational drug or device studies.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Written informed consent must be obtained prior to any screening procedures.
2. Patient is ≥ 18 years old at the time of informed consent.
3. Patient has histologically confirmed locally recurrent or metastatic predominantly clear cell renal cell carcinoma.
4. Patient must have measurable disease based on RECIST 1.1 criteria
5. Patient must have received prior systemic therapy with an immune checkpoint inhibitor (monotherapy or combination) as 1st or 2nd line RCC treatment. Note: patients with prior mTOR inhibitor or TKI treatment as monotherapy or in combination with immune checkpoint inhibitor are allowed; however, treatment with immune checkpoint inhibitor (monotherapy or in combination) must have been the last treatment prior to study entry.

[redacted]

6. Last dose of immune checkpoint inhibitor therapy must have been received 4 or more weeks before start of study treatment
7. For patients receiving treatment with bisphosphonates, patient must be on a stable, well-tolerated dose for at least 4 weeks prior to start of study treatment
8. Patient must meet the following laboratory values at the screening visit:
   - Absolute Neutrophil Count $\geq 1.5 \times 10^9$/L
   - Platelets $\geq 100 \times 10^9$/L
   - Hemoglobin ≥ 9 g/dL
   - Potassium, sodium, calcium and magnesium within normal limits of the central laboratory
   - Serum creatinine <1.5 mg/dL
     - OR if >1.5 mg/dL; calculated creatinine clearance ≥40 mL/min or eGFR >30 mL/min/1.72m^2
   - Urine Protein to Creatinine Ratio (UPC) <1
     - OR if UPC ≥ 1, then 24-hour urine protein <1 g

   Note: Use of urine dipstick for renal function assessment is not acceptable.
   - Total bilirubin ≤1.5 x ULN
   - Aspartate transaminase (AST) < 2.5 x ULN
   - Alanine transaminase (ALT) < 2.5 x ULN
9. Patient must have a Karnofsky performance status ≥70%.
10. Patient is able to swallow and retain oral medication in the form of tablets or capsules.
11. Normal ECG defined as the following:
    - Resting heart rate 50-90 bpm
    - QTcF at screening <450 ms (male patients), <460 ms (female patients)

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Renal cell carcinoma without any clear (conventional) cell component
2. History or clinical evidence of central nervous system (CNS) metastases.
   - Note: Patients who have previously-treated CNS metastases (surgery ± radiotherapy, radiosurgery, or gamma knife) and meet all 3 of the following criteria are eligible:
     a. Asymptomatic and,
     b. Have had no evidence of active CNS metastases for ≥6 months prior to enrollment and,
     c. Have no requirement for steroids or enzyme-inducing anticonvulsants (EIAC)
3. Prior treatment with pazopanib
4. Prior treatment with bevacizumab that was not given in combination with immune checkpoint inhibitor therapy.
5. Prior treatment with more than 2 lines of therapy (combination treatments are considered 1 line of therapy)

[redacted]

6. Patient has not recovered from toxicity from prior immune checkpoint inhibitor therapy. Recovery is defined as ≤ NCI-CTCAE Grade 1, except for LFT levels which must be <Grade 1.
7. Disease recurrence less than 6 months from the last dose of prior neoadjuvant or adjuvant therapy (including VEGF-R TKI)
8. Radiation therapy within 2 weeks of starting study treatment; however, prior palliative radiotherapy to metastatic lesion(s) is permitted provided there is at least one measurable lesion that has not been irradiated.
9. Concurrent therapy given to treat cancer including treatment with an investigational agent or concurrent participation in another clinical trial involving anti-cancer investigational drug.
10. Patients receiving prohibited concomitant medications that cannot be discontinued or replaced by safe alternative medication at least 5 half-lives of the concomitant medication or 7 days, whichever is longer, prior to the start of pazopanib treatment (refer to Section 6.3.3 for prohibited concomitant medications which are inducers and/or strong inhibitors of CYP3A4 isoenzyme).
11. Administration of any investigational drug within 4 weeks prior to the first dose of study treatment
12. Grade 3 hemorrhage within 4 weeks of starting study treatment.
13. Uncontrolled hypertension (defined as systolic blood pressure (SBP) of ≥140 mm Hg or diastolic blood pressure (DBP) of ≥90 mm Hg)
14. Cardiac or cardiac repolarization abnormality, including any of the following:
    - History of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to starting study treatment
    - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g,. bifascicular block, Mobitz type II and third degree AV block)
    - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
        - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
        - Inability to determine the QTcF interval
        - History of Class III or IV congestive heart failure, as defined by the New York Heart Association Classification of Congestive Heart Failure
        - Concomitant medication with a "Known risk of Torsades de Pointes" per www.qtdrugs.org that cannot be discontinued or replaced by safe alternative medication within 7 days prior to starting study drug
15. 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

[redacted]

- 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

16. 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
    - Active diarrhea of any grade
17. History of cerebrovascular accident include transient ischemic attack, 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.
18. History of human immunodeficiency virus (HIV) infection
19. History of chronic active hepatitis including subjects who are carriers of hepatitis B virus (HBV) or hepatitis C virus (HCV)
20. Major surgery within 4 weeks of starting study treatment
21. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the subject inappropriate for entry into the study.
22. Pregnant or nursing (lactating) women
23. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, are excluded **unless** they are using highly effective methods of contraception during dosing and for 2 weeks after stopping medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

      In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

[redacted]

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

24. Sexually active males unless they use a condom during intercourse while taking the drug during treatment and for 2 weeks after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen.
25. Patients with known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib.

6 Treatment

6.1 Study treatment

Pazopanib monohydrochloride salt is supplied as aqueous film-coated tablets containing 200 mg or 400 mg of the free base. Refer to the pazopanib Investigator's Brochure for information regarding the physical and chemical properties of pazopanib and a list of excipients.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Pazopanib	Tablets for oral use	800 mg QD	Daily

Pazopanib will be administered as a flat-fixed dose and not by body weight or body surface area. One cycle is equivalent to 28 days or 4 weeks.

Patients must be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel must ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed.

Pazopanib must be taken as follows:

- Patients should take pazopanib daily at approximately the same time each day in the morning.
- Pazopanib must be taken without food at least 1 hour before or 2 hours after meals.
- Patients should be instructed to swallow the pazopanib tablets whole and not to chew or crush them.
- If vomiting occurs during the course of treatment, patients should not take pazopanib again before the next scheduled dose.

[redacted]

- If a dose is missed, the subject should take the dose as soon as possible, but only if there are 12 or more hours remaining 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.

6.1.2 Treatment duration

Patients may continue on study treatment until 2 years after the last patient is enrolled. Patients may be discontinued from treatment with study drug earlier due to unacceptable toxicity, disease progression and/or treatment discontinuation at the discretion of the investigator or the patient. For patients, who in the opinion of the investigator are still deriving clinical benefit from pazopanib, every effort will be made to continue provision of study treatment through another program.

6.1.2.1 Dose escalation guidelines

Not applicable

6.1.3 Starting dose rationale

Votrient (pazopanib) is approved for the treatment of patients with advanced renal cell carcinoma (RCC). The recommended and approved starting dose is 800 mg orally once daily which is the starting dose that will be used in this study.

6.1.4 Provisional dose levels

Not applicable

6.2 Dose modifications

6.2.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow patients to continue the study treatment.

These dose modifications are summarized in Table 6-2. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2 or listed in Section 6.2.1.1.

These dose changes must be recorded on the Dosage Administration Record CRF.

Each patient is only allowed 2 dose reductions. In addition, a patient must discontinue treatment with pazopanib if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity.

If a patient requires a dose interruption of >21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study treatment. Patients who discontinue study treatment for a study related adverse event or an abnormal laboratory value must be followed as described in Section 8.1.

[redacted]

Table 6-2 Criteria for dose reduction / interruption and re-initiation of pazopanib treatment for adverse drug reactions

Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm3)	Recommendation: maintain dose level, monitor as clinically indicated
Grade 2 (ANC < 1500 - 1000/mm3)	Recommendation: maintain dose level, monitor as clinically indicated
Grade 3 (ANC < 1000 - 500/mm3)	Recommendation: Step 1: Omit dose until resolved to ≤ Grade 2 Step 2: Restart pazopanib at a dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 neutropenia, discontinue pazopanib and follow-up per protocol
Grade 4 (ANC < 500/mm3)	Mandatory: Step 1: Omit dose until resolved to ≤ Grade 2 Step 2: Restart pazopanib at a dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 4 neutropenia, discontinue pazopanib and follow-up per protocol
Febrile neutropenia (ANC < 1000/mm^3, fever ≥ 38.5°C)	Mandatory: Omit dose until resolved, then restart pazopanib at a dose reduced by 200 mg
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm3)	Recommendation: maintain dose level, monitor as clinically indicated
Grade 2 (PLT < 75,000 - 50,000/mm3)	Recommendation: maintain dose level, monitor as clinically indicated
Grade 3 (PLT < 50,000 - 25,000/mm3)	Recommendation: Step 1: Omit dose until resolved to ≤ Grade 2 Step 2: Restart study drug at a dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 thrombocytopenia, discontinue pazopanib and follow-up per protocol
Grade 4 (PLT < 25,000/mm3)	Mandatory: Step 1: Omit dose until resolved to ≤ Grade 2 Step 2: Restart pazopanib at a dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 thrombocytopenia, discontinue pazopanib and follow-up per protocol
Investigations (Renal)	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Recommendation: Maintain dose level

[redacted]

Grade 2 (> 1.5 - 3.0 x ULN)	Recommendation: Omit dose until resolved to ≤ Grade 1 or baseline, then maintain dose level
Grade 3 (> 3.0 - 6.0 x ULN)	Recommendation: Omit dose and permanently discontinue patient from pazopanib
Grade 4 (> 6.0 x ULN)	Mandatory: Omit dose and permanently discontinue patient from pazopanib
Proteinuria	
UPC <3	Recommendation: Continue study drug at the current dose; monitor as clinically indicated
UPC ≥3 or 24-h urine protein ≥3g	Mandatory: Step 1. Interrupt pazopanib. Step 2. Weekly monitoring with UPC or 24-hr urine total protein until UPC is <3 or 24-hr urine total protein is <3g, then restart pazopanib with dose-reduced by 200 mg. If UPC ≥3 or 24-hr urine protein ≥ 3g recurs, repeat the above steps. Pazopanib should be permanently discontinued if UPC ≥3 or 24hr urine protein ≥ 3g persists when treating at 400 mg dose level.
Investigations (Hepatic)	
(A) ALT of ≤ 3.0 x ULN	Recommendation: Continue pazopanib at current dose.
(B) ALT >3.0xULN to ≤5.0xULN without bilirubin elevation (defined as total bilirubin[b] ≤2.0xULN, or direct bilirubin ≤35%) and without hypersensitivity symptoms (e.g., fever, rash)	Mandatory: 1. Interrupt pazopanib. 2. Monitor subject closely for clinical signs and symptoms for liver failure. Perform full liver panel[a] at least weekly until ALT is reduced to ≤ Grade 1 (3.0xULN). • Subject should permanently discontinue pazopanib if ALT does not recover to ≤3.0xULN within 6 weeks 1. If ALT recovers to ≤3.0xULN within 6 weeks, subject is eligible to be re-challenged at 400 mg daily. • It is desirable for the ALT level to have recovered to ≤ULN or plateaued before re-challenge to avoid discontinuation due to recurrence of ALT >3.0xULN. Discuss with study physician as needed. 2. Following re-challenge, monitor subject closely for clinical signs and symptoms. Perform full liver panel weekly for 4 weeks and, if stable, every other week for 4 weeks. **Recurrence Stopping Criteria:** If ALT elevation recurs to >3.0xULN, permanently discontinue pazopanib and monitor subject closely for clinical signs and symptoms; perform full liver panel LFTs weekly or more frequently if clinically indicated until ALT is reduced to ≤ULN or stabilized. If recurrent ALT elevation meets the criteria for Scenario D or Scenario E, report the event to Novartis as an SAE within 24 hours of learning of its occurrence and follow the instruction under Scenario (D) or Scenario (E) of this table as indicated below accordingly

[redacted]

(C) ALT >5.0xULN to ≤8.0xULN **without** bilirubin elevation (defined as total bilirubin[b] ≤2.0xULN, or direct bilirubin ≤35% and **without** hypersensitivity symptoms (e.g., fever, rash)	Mandatory: 1. Interrupt pazopanib. 2. Monitor subject closely for clinical signs and symptoms of liver failure. Perform full liver panel weekly or more frequently if clinically indicated until ALT is reduced to ≤3.0xULN.Liver imaging is optional and dependent upon clinical scenario. • Subject should permanently discontinue pazopanib if ALT does not recover to ≤3.0xULN within 2 weeks 3. If ALT recovers to ≤3.0xULN within 2 weeks, subject is eligible to be re-challenged at 400 mg daily • It is desirable for the ALT level to have recovered to ≤ULN or plateaued before re-challenge to avoid discontinuation due to recurrence of ALT >3.0xULN. Discuss with study physician as needed. 4. Following re-challenge, monitor subject closely for clinical signs and symptoms; perform full liver panel weekly for 4 weeks and, if stable, every other week for 4 weeks. Recurrence Stopping Criteria: If ALT elevation recurs to >3.0xULN, permanently discontinue pazopanib and monitor subject closely for clinical signs and symptoms; perform full liver panel weekly or more frequently if clinically indicated until ALT is reduced to ≤ULN or stabilized. If recurrent ALT elevation meets the criteria for Scenario D or Scenario E, report the event to Novartis as an SAE within 24 hours of learning of its occurrence and follow the instruction under Scenario (D) or Scenario (E) of this table as indicated below accordingly.
(D) ALT >8.0xULN **without** bilirubin elevation (defined as total bilirubin[b] ≤2.0xULN, or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	Mandatory: 1. Permanently discontinue pazopanib. 2. Report the event to Novartis as an SAE within 24 hours of learning of its occurrence and complete the eCRF liver event forms. 3. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries. Monitor subject closely for clinical signs and symptoms; perform full liver panel weekly or more frequently if clinically indicated until ALT is recovered to ≤ULN or stabilized. 4. Liver imaging is optional and dependent upon clinical scenario. Perform liver imaging if the subject exhibits a possible biliary event (e.g., abdominal pain lasting for hours, fever, jaundice, palpable right upper quadrant mass).

[redacted]

(E) ALT >3.0xULN **with** concomitant elevation in bilirubin[b] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash). Note: if ALT >3.0xULN with concomitant total bilirubin >2.0xULN, but bilirubin fractionation is not available, the liver event should also be considered as category E.	Mandatory: 1. Permanently discontinue pazopanib. 2. Report the event to Novartis as an SAE within 24 hours of learning of its occurrence and complete the eCRF liver event forms. 3. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and perform the following additional evaluations and procedures: • Consult a gastroenterologist / hepatologist. • Collect blood samples for the following laboratory assessments for exclusion of hypersensitivity and other contributing factors. The blood samples should be submitted to the local laboratory for analysis[c]: • Eosinophil count • Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus, herpes simplex virus (IgM antibody, heterophile antibody, or monospot testing) • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver-kidney microsomal antibodies. • Serum creatinine phosphokinase • Liver imaging is optional and dependent upon clinical scenario • Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis. 4. 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 SAE report form. Perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT is recovered to ≤ULN or stabilized.
(F) For isolated total bilirubin elevation[c] without concurrent ALT increases (defined as ALT <3 X ULN) and with no other signs or symptoms of liver injury)	Recommendation: 1. If total bilirubin elevation is ≤2.0xULN, continue current dose, no additional testing is required. 2. If total bilirubin is >2.0xULN, bilirubin fractionation must be performed. • If bilirubin is predominantly indirect (i.e. conjugated or direct bilirubin is ≤35%), continue pazopanib at current dose[c]. If direct (or conjugated) bilirubin is >35%, dose-interrupt and perform further evaluation for underlying cause of cholestasis. Based on the finding, investigator can then determine whether to continue on pazopanib

[redacted]

a. Full liver panel includes: ALT, AST, albumin, creatine kinase, total bilirubin, direct bilirubin, GGT and alkaline phosphatase. Coagulation tests should be performed as clinically indicated. b. Serum bilirubin fractionation must be performed if total bilirubin >2.0xULN. Serum bilirubin fractionation (direct bilirubin) shouldn't be of concern if total bilirubin is ≤2.0xULN. c. Pazopanib is known to inhibit UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury.	
Investigation (metabolic)	
Asymptomatic amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	Recommendation: maintain dose level, monitor as clinically indicated
Grade 2 (> 1.5 - 2.0 x ULN)	Recommendation: maintain dose level, monitor as clinically indicated
Grade 3 (> 2.0 - 5.0 x ULN)	Recommendation: Omit dose of until resolved to Grade ≤,1 or baseline then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then restart study drug at a dose reduced by 200 mg
Grade 4 (> 5.0 x ULN)	Mandatory: Omit dose and discontinue patient from study drug treatment.
Vascular disorders	
Hypertension	
(A) Asymptomatic and persistent[d] 140 ≤ SBP <160 mmHg, or 90≤ DBP <100 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	Highly recommended: Step 1. Continue pazopanib at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s)[e] to achieve and maintain a BP level of < 140/90 mmHg. If BP cannot be controlled to <140/90mmHg within 3 weeks after 2 or more different antihypertensive medication adjustments, dose reduction of pazopanib by 200 mg should be considered.
(B) Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg	Highly recommended: Step 1. Dose reduce by 200 mg or interrupt pazopanib as per clinical judgment Step 2. Adjust current or initiate new antihypertensive medication(s)[e] to achieve and maintain a BP level of < 140/90 mmHg. If BP can be controlled to < 140/90mmHg within 3 weeks and pazopanib has been interrupted, it can be resumed with dose reduced by 200 mg from the pre-event dose. If BP cannot be adequately controlled with these measures, consider referring the subject to a specialist for further evaluation and management.
(C) Symptomatic hypertension or recurring SBP≥160 mmHg, or DBP≥100 mmHg, despite modification of antihypertensive medication(s)	Highly recommended: Step 1. Interrupt pazopanib Step 2. Strongly recommend referring the subject to a specialist for further evaluation and management Once BP is controlled to <140/90mmHg via adjustment of current or initiating new antihypertensive medication(s)[e], pazopanib can be resumed with dose reduced by 200 mg. BP should be monitored as clinically indicated

[redacted]

(D) Refractory hypertension unresponsive to above interventions including malignant hypertension, hypertensive crisis, transient or permanent neurological deficit related to uncontrolled hypertension.	Mandatory: Permanently discontinue pazopanib and continue follow-up per protocol.
d. Persistent SBP and/or DBP is defined as SBP of ≥140 or DBP ≥90 for at least 24 hours per NCI-CTCAE v4.03 Recommendation of antihypertensive agents for treatment-emergent BP elevations: ACE inhibitors, angiotensin receptor blocking agents, beta blockers, calcium channel blockers and diuretics have all shown to reduce blood pressure in subjects treated with pazopanib	
Gastrointestinal	
Pancreatitis	
Grade 2	Recommendation: Maintain dose level
Grade ≥ 3	Mandatory: Omit dose and discontinue patient from pazopanib
Diarrhea**	
Grade 1	Recommendation: Maintain dose level but, initiate anti-diarrhea treatment
Grade 2	Recommendation: Omit dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then reduce dose by 200 mg. Omit dose until resolved to ≤ grade 1, then reduce dose by 200 mg
Grade 3	Recommendation: Omit dose and discontinue patient from pazopanib
Grade 4	Mandatory: Omit dose Mandatory: Discontinue patient from pazopanib
Skin and subcutaneous tissue disorders	
Rash/photosensitivity	
Grade 1	Recommendation: Maintain dose level. Consider to initiate institute appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 2	Recommendation: Maintain dose level, but initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 3, despite skin toxicity therapy	Recommendation: Omit dose until resolved to Grade ≤ 1, then: If resolved in ≤ 7 days, then reduce dose by 200 mg. If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment
Grade 4, despite skin toxicity therapy	Mandatory: Omit dose Mandatory: Discontinue patient from study drug treament
Fatigue/ Asthenia (General disorders and administration site conditions)	
Grade 1 or 2	Recommendation: Maintain dose level

[redacted]

Grade 3	Recommendation: Omit dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then reduce dose by 200 mg
Hemorrhage/Bleeding: Investigate and document underlying etiology of the bleeding	
Grade 1	Recommendation: For hemoptysis, interrupt pazopanib and contact the Medical Monitor to discuss whether further treatment with pazopanib is appropriate. For other Grade I hemorrhage/bleeding events, continue pazopanib at the current dose; monitor as clinically indicated.
Grade 2	Recommendation: For pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue pazopanib and continue follow-up per protocol. For other G2 hemorrhage/bleeding events, interrupt pazopanib until the AE resolved to ≤ Grade 1. Restart pazopanib dose reduced by 200 mg, monitor as clinically indicated
Grade 3 or 4, or Recurrent ≥ Grade 2 event after dose interruption/reduction.	Mandatory: Permanently discontinue pazopanib and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 1	Recommendation: Continue pazopanib at the current dose; monitor as clinically indicated
Grade 2 or 3	Recommendation: Step 1: Interrupt pazopanib Step 2: Initiate and monitor anticoagulation as clinically indicated. Step 3: Resume pazopanib (reduced by 200 mg) 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 pazopanib. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in pazopanib dosing (e.g., 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	Mandatory: Permanently discontinue pazopanib and follow-up per protocol.

[redacted]

Arterial Thrombosis/Ischemia	
Any Grade	Mandatory: Permanently discontinue pazopanib and follow-up per protocol.
Cardiac	
Prolongation of QTcF Interval: If a QTcF reading is ≥ 500 msec, the ECG should be manually read to ensure accuracy of the reading	
480 < QTcF <500 msec	Recommendation: Continue pazopanib; monitor as clinically indicated
QTcF ≥ 500 msec	Mandatory: Permanently discontinue pazopanib and follow up per protocol. Patient must be monitored closely in a hospital setting until a cardiologist's evaluation has been obtained.
Other clinically significant non-liver related adverse events	
Grade 1	Recommendation: 1: Continue pazopanib at current dose 2: Manage the side effects with appropriate medical treatments/supportive care. A dose reduction of 200 mg may be considered if a subject experiences multiple Grade 1 AEs and cannot tolerate the current dose level
Grade 2	Recommendation 1: Manage side effects with appropriate medical treatments/supportive care 2: A dose reduction of 200 mg or interruption of pazopanib may be considered if a subject experiences a clinically significant Grade 2 AE or multiple Grade 2 and 1 AEs and cannot tolerate the current dose level If AEs are fully resolved or recover to Grade 1, the dose can be escalated to the pre-event level or maintained at the current level. For subjects with dose interruption, dose can be resumed at the pre-event level or dose-reduced by 200 mg based on clinical judgement
Grade 3	Recommendation: 1: Interrupt pazopanib 2: Manage the side effects with appropriate medical treatments/supportive care If AEs fully recover or recover to Grade 1, restart pazopanib with dose-reduced by 200 mg. Monitor as clinically indicated for AE recurrence. Dose can be interrupted or further reduced for recurrent G3 AEs
Grade 4	Recommendation: Permanently discontinue pazopanib and follow up per protocol
All dose modifications should be based on the worst preceding toxicity. **Common Toxicity Criteria for Adverse Events (CTCAE Version v4.03)** **** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea**	

[redacted]

Table 6-3 Dose reduction steps for pazopanib

	Pazopanib dose	Number of tablets & strength
Starting dose	800 mg QD	2 x 400 mg tablets
First dose reduction	600 mg QD	1 x 400 mg tablet and 1 x 200 mg tablet
Second dose reduction	400 mg QD	1 x 400 mg tablet

6.2.1.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

These patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 24 to 72 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct bilirubin, GGT, alkaline phosphatase and prothrombin time (PT)/INR.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection must be performed. Liver imaging (e.g., biliary tract) may be warranted.
4. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis must be performed. Liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.
5. Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

   Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

All cases meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and must be reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

[redacted]

6.3 Concomitant medications

During screening, all patients will be asked to provide a complete list of prescription and over-the-counter medications that the patient is taking. If a patient is taking any medications prohibited per protocol, the investigator should determine whether those medications can be replaced with other medications for the same indication.

A subject will be ineligible if he/she is unable or unwilling to discontinue use of prohibited medications (primarily strong CYP3A4 inhibitors and strong CYP3A4 inducers) for at least five half-lives of the prohibited medication, or 7 days, whichever is longer, prior to the first dose of study treatment and for the duration of the study.

For subjects with on-going AEs or new AEs within the 30 days post-treatment period, concomitant medications will be collected for the same period. Concomitant medications will not be collected beyond this point.

6.3.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF.

6.3.2 Permitted concomitant therapy requiring caution and/or action

Pazopanib is a potential inhibitor for CYP3A4, CYP2C8, and CYP2D6. The concomitant use of pazopanib with certain medications (substrates of CYP3A4, CYP2C8, and CYP2D6) with a narrow therapeutic window should be undertaken with **CAUTION** [See Appendix 1]. In addition, the potential for drug interaction with such medications, although diminished, may persist after the last dose of pazopanib due to its long half-life (i.e., mean 30.9 hours); therefore, continue to exercise **CAUTION** for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications.

6.3.2.1 Specific recommendations regarding the use of simvastatin and other statins

Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations. If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for pazopanib dose modification and discontinue simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

6.3.2.2 Specific recommendations regarding anticoagulants

Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib has no effect on the metabolism of S-warfarin. Hemorrhagic events, however, have been reported in clinical studies with pazopanib; therefore, pazopanib should be used with caution in subjects with increased risk of severe bleeding or who are receiving concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin). Subjects taking concomitant anticoagulant therapy should be

[redacted]

monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes.

6.3.2.3 Specific recommendations regarding hypoglycemic therapy including insulin

Results from drug-drug interaction studies conducted in subjects with cancer suggest that clinically relevant pharmacokinetic interaction between pazopanib and hypoglycemic agents is not expected. Transient decreases in serum glucose (mainly Grade 1 and 2, rarely Grade 3) have been observed in clinical studies with pazopanib. In addition, decreases in blood sugar have been recently reported in subjects treated with another small molecule tyrosine kinase inhibitor, sunitinib (Billemont 2008). Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

6.3.3 Prohibited concomitant therapy

Pazopanib metabolism is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8.

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. Co-administration of strong CYP3A4 inhibitors is prohibited; therefore selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended.

CYP3A4 inducers may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended.

A subject will be ineligible if he/she is unable or unwilling to discontinue use of prohibited medications for at least five half-lives or 7 days, whichever is longer, prior to the first dose of study treatment and for the duration of the study. A list of prohibited medications is included in Appendix 1.

Subjects should not receive other anti-cancer therapy [cytotoxic, biologic, radiation, or hormonal] prior to established disease recurrence in the study.

6.3.3.1 Drugs with QT prolongation

In the clinical RCC studies of pazopanib (VEG102616, VEG105192, VEG107769), QT prolongation (≥500 msec) was identified on routine ECG monitoring in less than 2% (11/558) of patients. Review of the cardiac safety in 11 pazopanib monotherapy studies, amounting to data on 977 patients, indicated that Torsade de pointes occurred in less than 1 % (2/977) of the patients. However, co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential drug-drug interaction (DDI) that increases the exposure of pazopanib or the exposure of the QT prolonging drug) should be avoided.

If during the course of the study, concomitant administration of drugs with a "Known risk of Torsades de Pointes" is required and cannot be avoided, study drug must be interrupted. If,

[redacted]

based on the investigator assessment and clinical need, study treatment is resumed, close ECG monitoring is advised.

If during the course of the study, concomitant administration of a drug with "Possible risk" or "Conditional risk of Torsades de Pointes" is required, based on the investigator assessment and clinical need, study treatment may be continued under close ECG monitoring to ensure patient safety.

A list of drugs associated with QT prolongation and/or TdP is available online at www.qtdrugs.org.

6.3.4 Use of bisphosphonates (or other concomitant agents)

The use of bisphosphonates is allowed if patients have been on stable and well tolerated doses of bisphosphonate treatment for at least 4 weeks prior to the start of study treatment.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 2 days that the patient was not started on treatment.

6.4.2 Treatment assignment or randomization

The investigational treatment, pazopanib, will be provided to all participants of this single arm study and no randomization processes will apply. Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be enrolled via IRT to the treatment arm. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will be used to track enrollment of patients in 2nd and 3rd line to ensure that approximately 40 patients receive pazopanib as 2nd line treatment.

6.4.3 Treatment blinding

All study participants will be treated with pazopanib; therefore, blinding is not applicable.

[redacted]

6.5 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.5.1 Study treatment packaging and labeling

The study treatment, pazopanib, will be sourced as local commercial supply (in the locally approved formulation and packaging configuration) and labeled in the country when possible.

Study treatment labels for local commercial supply will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study treatment and strength) or randomization number if appropriate.

If the label has 2-parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

Pazopanib in different formulations and strengths can be used once they are approved.

6.5.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the Investigator's Brochure.

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

[redacted]

6.5.3.3 Handling of other study treatment

Not applicable

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X" the visits when they are to be performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which data assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) (see Table 7-1 "Category" column).

No eCRF will be used as a source document.

- Screening assessments, apart from those listed below, must occur within 28 days prior to Cycle 1 Day 1 as per Table 7-1.
  - Physical exam, Karnofsky performance status, height, weight, vital signs, hematology, chemistry (LFT and other), thyroid panel, coagulation, urinalysis, pregnancy test, ECG, cardiac imaging and PRO questionnaires should be performed within 7 days prior to Cycle 1 Day 1. All other screening assessments must be completed within 28 days prior to Cycle 1 Day 1. Every effort should be made to follow the schedule.
- For all visits there is a ±3 day window on assessments to take into account scheduling over weekends and public holidays.
- Radiological assessments must be performed as outlined in Table 7-1. A visit window of ± 7 days is allowed.
- Efficacy follow up will only be performed in patients who discontinue study treatment without disease progression by RECIST 1.1 before LPFV + 1 year.
- Survival follow up will be performed in all patients. For patients who enter the efficacy follow up, survival follow up will not begin until after the efficacy follow up is completed. For patients who discontinue study treatment due to disease progression at any time or for any reason after LPFV + 1 year, survival follow-up will begin after end of treatment.

[redacted]

Table 7-1 Visit evaluation schedule

			SCREENING PHASE		TREATMENT PHASE											FOLLOW UP PHASE		
Visit Name	Category	Protocol Section	Screening		C1			C2		C3	C4	C5	C6	Cycles 7, 9, 11, 13	Cycle 16 and every 3rd cycle thereafter until EOT	End of study treatment (EoT)	Safety follow up	Efficacy follow up until PD or until 1 year from LPFV	Survival follow up until 2 years from LPFV
Day of cycle			-28 to -1	-7 to -1	1	8	15	1	15	1	1	1	1	1	1		30 days following EOT	Every 8 weeks	Every 12 weeks
Informed Consent																			
Main Informed Consent	D	7.1.1.	X																
[redacted]																			
Patient history																			
Demography	D	7.1.1.3.	X																
Inclusion/exclusion criteria	D	5.2 & 5.3.		X															
Medical history	D	7.1.1.3.	X																
Diagnosis and extent of cancer	D	7.1.1.3.	X																
MSKCC criteria	D	7.1.1.3.1.		X															
Prior antineoplastic therapy (surgery, radiotherapy, medication)	D	7.1.1.3.	X																
Prior/concomitant medications	D	7.1.1.3.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

[redacted]

			SCREENING PHASE		TREATMENT PHASE												FOLLOW UP PHASE		
Visit Name	Category	Protocol Section	Screening		C1			C2		C3	C4	C5	C6	Cycles 7, 9, 11, 13	Cycle 16 and every 3rd cycle thereafter until EOT	End of study treatment (EoT)	Safety follow up	Efficacy follow up until PD or until 1 year from LPFV	Survival follow up until 2 years from LPFV
Day of cycle			-28 to -1	-7 to -1	1	8	15	1	15	1	1	1	1	1	1		30 days following EOT	Every 8 weeks	Every 12 weeks
IRT																			
IRT-screening/ discontinuation	S	7.1.1.1 & 7.1.3.	X													X			
IRT- eligibility checklist	S	7.1.1.1.		X															
Date of treatment assignment	S / D	6.4.2.			X														
Physical examination																			
Physical examination	S	7.2.2.1.		X				X		X	X	X	X	X	X	X			
Karnofsky Performance status	D	7.2.2.4.		X				X		X	X	X	X	X	X	X			
Height	D	7.2.2.3.		X															
Weight	D	7.2.2.3.		X			X	X	X	X	X	X	X	X	X	X			
Vital signs	D	7.2.2.3.		X		X	X	X	X	X	X	X	X	X	X	X			
Laboratory assessments																			
Hematology	D	7.2.2.5.1.		X				X			X		X	As clinically indicated		X			
Chemistry- LFT	D	7.2.2.5.2.		X			X	X	X	X	X	X	X	As clinically indicated		X			
Chemistry- other	D	7.2.2.5.2.		X				X			X		X	As clinically indicated		X			

[redacted]

			SCREENING PHASE		TREATMENT PHASE												FOLLOW UP PHASE		
Visit Name	Category	Protocol Section	Screening		C1			C2		C3	C4	C5	C6	Cycles 7, 9, 11, 13	Cycle 16 and every 3rd cycle thereafter until EOT	End of study treatment (EoT)	Safety follow up	Efficacy follow up until PD or until 1 year from LPFV	Survival follow up until 2 years from LPFV
Day of cycle			-28 to -1	-7 to -1	1	8	15	1	15	1	1	1	1	1	1		30 days following EOT	Every 8 weeks	Every 12 weeks
Thyroid Panel	D	7.2.2.5.5.		X				X			X		X	As clinically indicated		X			
Coagulation	D	7.2.2.5.4.		X	As clinically indicated											X			
Urinalysis	D	7.2.2.5.3.		X				X		X	X	X	X	X	X	X			
Urine Protein/ Creatinine ratio	D	7.2.2.5.6.		X	As clinically indicated											X			
24-hr urine collection	D	7.2.2.5.7.		As clinically indicated															
Serum Pregnancy test (if applicable)	D	7.2.2.5.8.		X												X			
Urine Pregnancy test (if applicable)	D	7.2.2.5.8.						X		X	X	X	X	Monthly at home					
Patient diary for pregnancy test	S	7.2.2.5.8.												Monthly at home					
Tumor assessments																			
Tumor evaluation	D	7.2.1.	X		Every 8 weeks during the first year and every 12 weeks thereafter											X		X	
Bone scan	S	7.2.1.	X	As clinically indicated															
Cardiac assessments																			
ECG	D	7.2.2.6.1.		X						X		X		X	X	X			

[redacted]

			SCREENING PHASE		TREATMENT PHASE												FOLLOW UP PHASE		
Visit Name	Category	Protocol Section	Screening		C1			C2		C3	C4	C5	C6	Cycles 7, 9, 11, 13	Cycle 16 and every 3rd cycle thereafter until EOT	End of study treatment (EoT)	Safety follow up	Efficacy follow up until PD or until 1 year from LPFV	Survival follow up until 2 years from LPFV
Day of cycle			**-28 to -1**	**-7 to -1**	**1**	8	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**1**		30 days following EOT	Every 8 weeks	Every 12 weeks
Cardiac imaging	D	7.2.2.6.2.		X								X		C11 only	C16 then every 6th cycle	X			
Safety																			
Adverse events	D	8.1.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Surgical/medical procedures	D	7.1.1.3.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hepatotoxicity follow-up	D	6.2.1.1.			As clinically indicated														

[redacted]

[redacted]

			SCREENING PHASE		TREATMENT PHASE												FOLLOW UP PHASE		
Visit Name	Category	Protocol Section	Screening		C1			C2		C3	C4	C5	C6	Cycles 7, 9, 11, 13	Cycle 16 and every 3rd cycle thereafter until EOT	End of study treatment (EoT)	Safety follow up	Efficacy follow up until PD or until 1 year from LPFV	Survival follow up until 2 years from LPFV
Day of cycle			**-28 to -1**	**-7 to -1**	**1**	8	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**1**		30 days following EOT	Every 8 weeks	Every 12 weeks
Patient Reported Outcomes																			
EuroQoL EQ-5D-5L	D	7.2.5.		X (predose)				X		X	X	X	X	X	X	X			
FKSI-DRS	D	7.2.5.		X (predose)				X		X	X	X	X	X	X	X			
Treatment																			
Study Drug administration	D	6.1.			Daily dosing														
Discontinuation																			
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5.															X	X	X
Survival Follow-up	D	7.1.5.3.																	X
Disposition																			
Study phase disposition	D	7.1.1, 7.1.3 & 7.1.5.2.		X												X		X	

[redacted]

7.1.1 Screening

Written informed consent must be obtained before any study specific procedure is performed.

Upon obtaining consent, the investigator or his/her delegate will register the patient in the IRT and provide the information requested by the system.

Screening assessments to confirm eligibility will be done within 1 to 28 days prior to treatment start date or within 1 to 7 days prior to treatment start date for selected assessments (see Table 7-1 for list of assessment to be performed).

Any screening assessment that is done outside the screening window (Day -28 to Day -1 or Day -7 to Day -1) must be repeated prior to the subject's first dose.

Re-screening of patients is permissible at the discretion of the investigator. Re-screening should only occur after a patient has failed screening. The same patient ID number should be used to re-screen. Re-screening should not occur more often than every 7 days. A re-screened patient may enter the study only if **all** inclusion and **no** exclusion criteria are met.

Imaging assessments previously performed as part of the patient's routine disease care, including those done before signing the main ICF, can be considered as the baseline images for the study if the assessments were done within 28 days prior to the start of treatment.

The Screening Phase Disposition eCRF page will be completed for all patients at the end of the screening phase.

7.1.1.1 Eligibility screening

Patients must meet all inclusion criteria (Section 5.2) and none of the exclusion criteria (Section 5.3) criteria during the screening phase in order to be eligible for the study.

In order to confirm the eligibility of the patient, an eligibility checklist must be completed via IRT by the investigator or designee once all screening procedures are completed and prior to the patient's first dose. Please refer to and comply with detailed guidelines in the IRT manual.

7.1.1.2 Information to be collected on screening failures

A patient who signs an informed consent but fails to satisfy all eligibility criteria for any reason will be considered a screen failure. The following information will be collected in the clinical database for all screening failures:

- Visit date
- Informed consent
- Demography
- Inclusion/Exclusion Criteria
- Screening Phase Disposition Page
- Adverse events (only if an SAE occurs- see Section 8 for SAE reporting details)
- Death (if applicable)
- Withdrawal of Consent (if applicable)

[redacted]

No other data will be entered into the clinical database for patients who are screen failures. Investigative staff must notify the IRT system of all screen failures, preferably within 2 days of the screen failure.

7.1.1.3 Patient demographics and other baseline characteristics

The following data will be collected on patient characteristics at screening, unless otherwise specified in the respective section:

- Demography (including: year of birth, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)
- Diagnosis and extent of cancer (including staging at study entry and histology/cytology)
- MSKCC risk score (refer to Section 7.1.1.3.1)
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History eCRF should include the toxicity grade.
- All prior antineoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for cancer prior to the administration of study drug.
- All medications and significant non-drug therapies taken within 30 days before the first dose is administered must be recorded on the Prior and Concomitant medication or Surgical and medical procedures eCRF page and updated on a continual basis if there are any new changes to the medications.
- Patient-reported outcome questionnaires (EQ-5D-5L and FKSI-DRS (See Section 7.2.5)). Baseline (i.e., screening period) questionnaires should not be administered until the patient is confirmed to be eligible for the study; questionnaires may be completed on Cycle 1 Day 1 prior to start of treatment.

Furthermore the following assessments will be performed:

- Vital signs
- Height, weight
- Physical examination
- Performance status (Karnofsky)
- Laboratory evaluations (hematology, chemistry, urinalysis, coagulation, thyroid, UPC, and 24-hr urine collection, if necessary, serum pregnancy test as applicable)
- ECG
- ECHO/MUGA
- Radiological assessments (e.g., CT Scan)
- Collection of archival tumor sample
- Collection of newly obtained tumor sample (optional)

[redacted]

7.1.1.3.1 Risk factors for MSKCC prognosis

The following prognostic criteria were identified in previously treated patients with advanced RCC (Motzer et al 2004):

- Karnofsky performance status (< 80%)
- Low serum hemoglobin (≤ 13 g/dL for males and < 11.5 g/dL for females)
- High corrected serum calcium (≥ 10 mg/dL)

Table 7-2 MSKCC prognostic criteria

Prognosis	Number of Risk Factors
Favorable	0
Intermediate	1
Poor	2 or 3

Motzer et al (2004).

7.1.2 Treatment period

Patients will be treated with pazopanib until disease progression, unacceptable toxicity, death, discontinuation from the study treatment due to any other reason or until two years after the last patient is enrolled. For details of assessments, refer to Table 7-1.

7.1.3 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time.

If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator may discontinue study treatment for a given patient if he/she believes that continuation would be detrimental to the patient's well-being.

In addition to mandatory dose interruptions and/or reductions of study treatment listed in Table 6-3, study treatment must also be discontinued under the following circumstances:

- Adverse event or lab abnormality as indicated in Section 6.2, or a dose interruption of more than 21 days
- Progressive disease
- Pregnancy
- Death
- Subject/guardian decision
- Lost to follow-up

Study treatment may also be discontinued if any of the following occur:

- Protocol deviation
- Study terminated by sponsor

[redacted]

- Technical problems
- Physician decision

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Table 7-1. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, email, letter) should be made to contact them as specified in Section 7.1.6.

Patients who discontinue study treatment should undergo an End of Study treatment visit followed by a 30 day safety follow-up. The "End of Treatment Phase Disposition" eCRF page must be completed, giving the date and primary reason for discontinuation.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent before LPFV + 1 year, tumor assessments must continue to be performed every 8 weeks until documented disease progression, death, lost to follow-up, withdrawal of consent or until one year from LPFV.

7.1.3.1 Replacement policy

Not applicable

7.1.4 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.1.5 Follow-up phases

7.1.5.1 Safety follow-up

All patients must have safety evaluations for 30 days after the last dose of study treatment.

Data collected should be added to the Adverse Events eCRF, the Surgical and Medical Procedures eCRF, the Concomitant Medications eCRF and the "Antineoplastic Therapy Since Discontinuation of Study Treatment" eCRF for the first antineoplastic therapy to be administered to the patient since study drug discontinuation.

[redacted]

Patients whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first. If patients refuse to return for safety evaluation visits or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the patient should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc.).

7.1.5.2 Efficacy follow-up

Patients who discontinue study treatment without disease progression by RECIST 1.1 before LPFV + 1 year will continue to be followed for efficacy every 8 weeks. In addition to the efficacy follow-up, the first antineoplastic therapy to be administered to the patient since study drug discontinuation will be documented on the "Antineoplastic Therapy Since Discontinuation of Study Treatment" eCRF pages. For further details, please refer to Table 7-1.

End of post-treatment follow-up (i.e., efficacy follow up) may occur due to one of the following reasons:

- LPFV + 1 year
- Adverse event
- Death
- Progressive disease
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- Technical problems
- Lost to follow-up
- Physician decision
- Subject/guardian decision

At that time, the patient will enter into the survival follow-up phase, if applicable, and the reason for completion of the efficacy follow-up phase will be recorded on the "End of Post Treatment Phase Disposition" eCRF page.

7.1.5.3 Survival follow-up

In order to assess overall survival, patients will be followed for survival every 12 weeks until the study ends (i.e., LPFV + 2 years). Patients, who discontinue study treatment without disease progression by RECIST 1.1 and enter the efficacy follow-up, will not begin the survival follow-up until after the efficacy follow-up period ends. Patients, who discontinue study treatment due to progression by RECIST 1.1 at any time or for any reason after LPFV + 1 year, will begin survival follow-up following end of treatment. Survival information can be obtained by clinical visits or telephone calls until death, lost to follow up, the patients withdraws consent for survival follow-up or the study ends. In addition to this survival follow-up, the first antineoplastic therapy to be administered to the patient since study drug discontinuation will be documented on the "Antineoplastic Therapy Since Discontinuation of Study Treatment" eCRF pages.

[redacted]

7.1.6 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be assessed locally according to the Novartis guideline version 3.1 (Appendix 2) based on RECIST 1.1 (Eisenhauer 2009).

Screening imaging assessments

Imaging assessments will be performed at screening within 28 days prior to the start date of treatment.

Any imaging assessments already completed during the regular work-up for the patient within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the screening images for this study.

The following imaging assessments are required at screening:

- Chest, abdomen and pelvis CT or MRI
- Whole body bone scan
- Brain CT or MRI, only if suspected brain metastases
- Localized bone CT, MRI or x-ray, for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI
- CT or MRI of other metastatic sites (e.g., neck), if clinically indicated

If a patient is known to have a contraindication to CT intravenous contrast media or develops a contraindication during the trial, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed. MRI of the chest is not recommended due to respiratory artifacts; however, if CT is not feasible per local regulations, MRI can be performed instead.

If brain metastases are suspected during screening or at any time on study, brain MRI or CT should be completed. Contrast enhanced brain MRI is preferred; however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

A whole body scan should be performed per institutional standard of care [e.g., Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET) or sodium fluoride (NaF) PET]. Localized CT, MRI or X-rays should be acquired for all skeletal lesions identified on the screening whole body bone scan, which are not visible on the chest, abdomen and pelvis CT/MRI.

[redacted]

If clinically indicated, CT or MRI of other areas (e.g., neck) of disease as appropriate should be performed.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

Chest x-rays and ultrasound should not be used to measure tumor lesions.

Post-baseline imaging assessments

Imaging assessments as described in Table 7-3 should be performed at the time points specified using the same imaging modality used at screening. Imaging assessments for response evaluation will be performed every 8 weeks (± 7 days) during the first year, and every 12 weeks (± 7 days) thereafter until study treatment discontinuation for disease progression, death, lost to follow-up, withdrawal of consent or the end of the study. Imaging assessments should be scheduled using the treatment start date (Cycle 1 Day 1) as the reference date (not the previous tumor assessment date), and should be respected regardless of whether the study treatment is temporarily withheld or unscheduled assessments performed.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a subject, as necessary. Clinical suspicion of disease progression at any time requires a physician examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at screening must be measured by the same method and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Partial Response (PR) and Complete Response (CR) must be confirmed by repeat assessments performed not less than 4 weeks and after the criteria for response are first met. Positron Emission Tomography (PET)/CT may be used only if the CT component is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and i.v. contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Appendix 2). If possible, a single radiologist should perform all tumor response evaluations for an individual patient. Any lesions in previously irradiated areas should not be considered measurable unless they have experienced progression since the radiotherapy. Any pre-existing radiographic findings which may mimic metastatic disease and any prior radiotherapy should be recorded in the eCRF.

Results from tissue or body fluid collection should be recorded in the eCRF to complement radiographic findings.

If a patient discontinues treatment for reasons other than radiological documentation of progression of disease, an efficacy assessment should be performed at the time of End of

Treatment unless a CT/MRI for tumor measurement was performed within 21 days. Efficacy assessments should then continue as per the scheduled visits in Table 7-1 and Table 7-3.

For patients who discontinue treatment for reasons other than documented disease progression by RECIST 1.1, death, lost to follow-up, or withdrawal of consent before LPFV + 1 year, tumor assessments must continue to be performed every 8 weeks until documented disease progression, death, lost to follow-up, withdrawal of consent or until LPFV + 1 year.

The first subsequent anti-neoplastic therapy, including start/end date, will be captured in the antineoplastic therapy since discontinuation of treatment eCRF for all patients.

Table 7-3 Imaging assessment collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)	Mandated within 28 days prior to Cycle 1 Day 1	During treatment: Mandated, every 8 weeks (± 7 days) during first year and every 12 weeks (± 7 days) thereafter then at End of Treatment. During efficacy follow-up: Mandated, every 8 weeks (± 7 days) until PD or until 1 year from LPFV (whichever comes first)
Whole body bone scan	Mandated within 28 days prior to Cycle 1 Day 1	As clinically indicated
Brain CT or MRI	Only if suspected brain metastases	As clinically indicated
Localized bone CT, MRI or x-ray	For any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis. For any new lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI.
CT or MRI of other metastatic sites (e.g., neck)	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examinations, Karnofsky performance status, height and weight, vital signs, ECG, cardiac imaging, patient reported outcomes, laboratory assessments including hematology, chemistry, coagulation, thyroid panel, pregnancy testing and urinalysis. All adverse events, surgical and medical procedures and concomitant medications will be collected at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

The physical examination comprises a total body examination that should include: general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph-nodes, extremities, vascular and neurological review. If indicated, rectal, external genitalia, breast and pelvis exams will be performed. Information about the physical examination must be present in the source documentation at the study site. Physical examination is to be performed according to the visit schedule as outlined in Table 7-1.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or

[redacted]

worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature. Vital signs will be monitored as per the visit schedule (see Table 7-1).

7.2.2.3 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1.

7.2.2.4 Performance status

Performance status will be assessed according to the Karnofsky performance status scale (Table 7-4) following the schedule given in Table 7-1.

Table 7-4 Karnofsky performance status

Score (%)	Performance Status
100	Normal: no complaints
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance but is able to care for most of his needs
50	Requires considerable assistance and frequent medical care
40	Disabled: requires special care and assistance
30	Severely disabled: hospitalization is indicated though death not imminent
20	Very sick; hospitalization is necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

7.2.2.5 Laboratory evaluations

Clinical laboratory analyses (hematology, chemistry, coagulation, thyroid panel, UPC, 24-hr urine collection and pregnancy testing) will be performed by the central laboratory. Dipstick urinalysis and urine pregnancy testing will be performed locally with materials supplied by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Visit windows of ±3 days are allowed.

In order to monitor patients' safety during the study, the laboratory assessments outlined in the protocol are the minimum requirement. Some patients may need more frequent laboratory assessments or other specific laboratory testing. Additional laboratory testing may be performed centrally or at a local laboratory, in emergency situations. Hepatotoxicity follow-up testing (described in Table 6-2, Table 7-5 and Section 6.2.1.1) must be done locally.

[redacted]

Whenever local laboratory assessments (i.e., for any unscheduled laboratory assessments), Novartis must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the new effective date. Additionally, if at any time a patient has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the Common Terminology Criteria for Adverse events (NCI-CTCAE) version 4.03. Additional analyses are left to the discretion of the investigator.

Unless specified in Table 7-5, all laboratory analyses will be performed centrally and the central results will be electronically transferred to the database.

Table 7-5 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	White blood cells, Hemoglobin, Platelets, Differential (Neutrophils, Lymphocytes, Eosinophils, Basophils, Monocytes, Bands, Other)
Chemistry- LFT	Liver function tests: Alkaline phosphatase (ALP), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Direct Bilirubin, Total Bilirubin
Chemistry- other	Albumin, Calcium, Magnesium, Phosphate, Sodium, Potassium, Total Cholesterol, Creatinine, Blood Urea Nitrogen (BUN) or Urea, Amylase, Lipase, Glucose (fasting or non-fasting), LDH, Uric acid, Creatinine kinase
Urinalysis[1]	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein)
Coagulation	International normalized ratio [INR], Activated partial thromboplastin time (APTT) in secs, Activated partial thromboplastin time (APTTP) in %
Thyroid[2]	T3 [free], T4 [free], TSH
Urine Protein/ Creatinine ratio (UPC)	At screening, end of treatment and as clinically indicated.
24-hr urine collection	Total urine volume collected, urine creatinine excretion, urine protein excretion, total urine creatinine clearance to be done as clinically indicated.
Pregnancy Test[1,3]	Serum pregnancy test is required at screening and end of treatment. Monthly urine pregnancy testing is required during treatment. Urine pregnancy tests will be conducted locally during site visits on Day 1 of Cycles 2 through 6. After Cycle 6, patients will be required to perform monthly at-home urine pregnancy tests which will be recorded on a patient diary.

[redacted]

Test Category	Test Name
Viral hepatitis serologic tests and other tests for hepatotoxicity follow-up[4]	Liver Event – Autoimmune:: Anti-smooth muscle antibodies, ANA titer, LKM-1 antibodies, Anti-SLA antibodies, Antinuclear antibodies – pattern Liver Event - Immunoglobulin: Immunoglobulin G, M, E, A Liver Event - Viral Serology: Anti-HAV IgM (coded[5]), HAV Total Serology, HBsAg, Anti-HBc IgM (coded), HBV DNA (coded), HCV antibody, HCV-RNA (coded), HDV RNA (coded), Anti-HEV IgM (coded), HEV IgG (coded), HEV-RNA (coded), Anti-EBV IgM (coded), Anti-HSV IgM (coded), Anti-CMV IgM (coded) Liver Event - Liver Function Tests: AST (SGOT), ALT (SGPT), Alkaline phosphatase, GGT, 5 Prime nucleotidase, Bilirubin (total), Direct bilirubin, Albumin, Prothrombin time, Prothrombin time % (Quicks test), INR, LDH, Eosinophils (%), Eosinophils (absolute), Creatine kinase (Creatine phosphokinase)

[1] Urinalysis as well as the on-site urine pregnancy testing will be done locally with materials provided by the central laboratory. Urinalysis results must be entered on the eCRF.
[2] Interference with Total T3 and Free T4 assays may be observed in patients taking high doses of biotin. It is recommended any biotin supplements be stopped for 3 days prior to sampling.
[3] At home pregnancy test kits will be provided by the investigator.
[4] Hepatotoxicity follow-up testing/procedures will be performed locally, where locally available.
[5] Wherever indicated, "(coded)" means a qualitative result (negative or positive) is required.

7.2.2.5.1 Hematology

Hematology tests are to be performed centrally according to the Visit Evaluation Schedule outlined in Table 7-1. For details of the hematology panel refer to Table 7-5.

7.2.2.5.2 Clinical chemistry

Clinical chemistry tests are to be performed centrally according to the Visit Evaluation Schedule outlined in Table 7-1. For details of the chemistry panels, refer to Table 7-5.

7.2.2.5.3 Urinalysis

Urinalysis using a dipstick is to be performed locally with materials supplied by the central lab. For details of the test, refer to Table 7-5.

7.2.2.5.4 Coagulation

Coagulation is to be performed centrally according to the Visit Evaluation Schedule outlined in Table 7-1. For details of the coagulation panel, refer to Table 7-5.

7.2.2.5.5 Thyroid

Thyroid panel is to be performed centrally according to the Visit Evaluation Schedule outlined in Table 7-1. For details of the thyroid panel, refer to Table 7-5.

7.2.2.5.6 Urine protein/creatinine ratio

UPC is to be performed centrally according to the Visit Evaluation Schedule outlined in Table 7-1.

[redacted]

7.2.2.5.7 24-hour urine collection

24-hour urine collection is to be performed according to the Visit Evaluation Schedule outlined in Table 7-1. Urine will be collected over a 24-hour period using materials supplied by the central lab. The analysis of the 24-hour urine collection will be performed centrally.

7.2.2.5.8 Pregnancy testing

Serum pregnancy tests are required at screening and end of treatment for women of child-bearing potential.

Monthly urine pregnancy testing is required during treatment for women of child-bearing potential. Urine pregnancy tests for use during on-site visits will be supplied by the central lab and will be performed locally during site visits on Day 1 of Cycles 2 through 6. After Cycle 6, women of child-bearing potential will be required to perform monthly at-home urine pregnancy tests. At-home pregnancy test kits will be supplied by the investigator. Patients who administer the urine pregnancy test at home will complete a simple diary with the dates and outcome of the urine pregnancy test while on study treatment. Patients should be instructed to bring the diary with them to every visit.

Please refer to the Section 5.3 for the definition of women of child-bearing potential.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed locally at the time points indicated in Table 7-6 below. ECGs should be done after the patient has been resting for 5-10 min prior to each time point.

Unscheduled ECGs may be performed at the discretion of the investigator at any time during the study and as clinically indicated.

Table 7-6 Local ECG collection plan

Cycle/Visit	Day	Time point	ECG Type
Screening	-7 to -1	Anytime	12 Lead
3	1	Anytime	12 Lead
5	1	Anytime	12 Lead
7	1	Anytime	12 Lead
9	1	Anytime	12 Lead
11	1	Anytime	12 Lead
13	1	Anytime	12 Lead
Cycle 16 and every 3rd cycle (i.e. cycle 19, 22, 25, etc.) and End of Treatment	1	Anytime	12 Lead
Unscheduled		Anytime	12 Lead

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the Medical

[redacted]

History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page. Refer to Table 6.2 for additional monitoring requirements if the QTcF interval is ≥ 500 msec.

7.2.2.6.2 Cardiac imaging- multiple gated acquisition (MUGA) scan or echocardiogram (ECHO)

Cardiac imaging will be performed locally by MUGA scan or ECHO in order to assess the left ventricular ejection fraction. This assessment will be performed according to the schedule indicated in Table 7-7 below.

Unscheduled cardiac imaging may be performed at the discretion of the investigator at any time during the study and as clinically indicated. Patients should be closely monitored for signs and symptoms of congestive heart failure. In particular, patients at risk of cardiac dysfunction or with prior anthracycline exposure may warrant more frequent monitoring.

Table 7-7 Local cardiac imaging collection plan

Cycle/Visit	Day	Time point
Screening	-7 to -1	Anytime
5	1	Anytime
11	1	Anytime
Cycle 16 and every 6th cycle thereafter (i.e., cycles 22, 28 etc.) and End of Treatment	1	Anytime
Unscheduled	Anytime	Anytime

[redacted]

[redacted]

[redacted]

[redacted]

7.2.4 Resource utilization

Not applicable.

7.2.5 Patient reported outcomes

Patient reported outcomes (PROs) provide patients, physicians, and payers with valuable information about the impact of a given treatment on all facets of the patient's life. PRO measures for use in clinical trial assess symptoms, functioning, health related quality of life and quality of life or a combination of these outcomes.

Both questionnaires (EQ-5D-5L and FKSI-DRS) will be provided electronically (ePRO) and are to be completed by the patient.

Both questionnaires must be completed during the screening phase within 7 days before the first dose of study medication (pazopanib) only after patient eligibility is confirmed, or on Cycle 1 Day 1 predose. During the treatment phase, both questionnaires should be completed on Day 1

[redacted]

of every cycle until Cycle 7 and then every 2nd cycle until Cycle 16 and then every 3rd cycle thereafter until the end of study medication treatment.

The questionnaires should be completed in the language most familiar to the patient.

The investigator or designee will administer both questionnaires under the following conditions:

- upon arrival to the clinic, before the patient has their evaluation visit with the treating oncologist
- upon arrival to the clinic, before the patient has their radiological tumor evaluations (CT scan or MRI).

The patient should be given sufficient space and time to complete the questionnaires. The site staff should check the questionnaire for completeness and encourage the patient to complete any missing responses.

Completed questionnaire(s) and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in the study source records.

7.2.5.1 Euro QOL-EQ-5D-5L (EQ-5D-5L)

The EQ-5D-5L is a general health status and health utility measure (Rabin 2001). It measures 5 dimensions of health state: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression each assessed by a single question on a threepoint ordinal scale. It also includes a VAS scale to measure health state. The EQ-5D-5L will be included in this study for the purpose of the computation of utilities that can be used in health economic studies. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability (Pickard 2007).

7.2.5.2 FKSI-DRS

The Functional Assessment of Cancer Therapy - Kidney Symptom Index, Disease Related Symptoms (FKSI-DRS) is a set of items selected which was developed and validated to specifically assess symptoms experienced by patients with advanced kidney cancer (Cella 2007). Item development was conducted using both clinician and patient input to determine the 9 most important symptoms and concerns of people being treated for advanced kidney cancer. These 9 items were then validated by administering the symptom index to patients diagnosed with advanced kidney cancer. The symptoms covered by the 9-item FKSI-DRS include fatigue, pain, weight loss, dyspnea, cough, fever and hematuria. The FKSI-DRS will be scored according to the developers' instructions. A difference of 2-3.0 points is suggested by the developers to correspond to a meaningful difference in treatment effects using the 9 question tool.

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met

[redacted]

7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (i.e. as per RECIST criteria), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be

[redacted]

appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the Investigator's Brochure.

AESIs for this trial include hepatic toxicity, hypertension, thyroid-related disorders and cardiac disorders.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event
- Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (i.e. as per RECIST criteria), should not be reported as a serious adverse event.

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

[redacted]

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship of pazopanib to any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

[redacted]

The collection of this information could last up until to birth and potentially up to 12 months following the birth of the child in some cases.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator's Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g., has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned

[redacted]

user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Safety laboratory assessments [redacted] (blood and tissue) samples drawn during the course of the study will be collected from the investigator sites and sent to the Novartis designated central laboratory for processing. The site staff designated by the investigator will enter the information required by the protocol onto the sample collection eCRF, as well as onto the designated CRO's requisition form. One copy of the requisition form will be forwarded to the central lab along with the corresponding samples with required information (including study number, subject ID, etc.) and one copy will be retained by the site.

[redacted]

PRO data must be recorded by patients onto the electronic tablet device maintained at study site. The site will enter information regarding ePRO collection in the eCRF.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data (e.g., safety laboratory assessment [redacted] samples) will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

PRO data collected using an electronic tablet device will be documented into a separate study specific database supplied and managed by a designated vendor. All PRO data will be sent electronically to Novartis personnel (or a designated CRO).

Data about patient enrollment, discontinuation of study treatment, and medication numbers (if applicable) for study treatment dispensed via IRT (in countries that are supplied by Novartis DSM) will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

The occurrence of any protocol violations will be determined. After these actions have been completed and the data have been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The primary efficacy and safety analyses will be conducted after all patients have completed 6 cycles of study treatment or have discontinued early. The primary analysis will be summarized in the primary CSR based on the Full Analysis Set (FAS). The final analysis will be performed at the end of the study and will be summarized in the final study CSR. Data analysis cut-off dates will be determined and the primary and the final analyses, and all data captured in the study up to the respective cut-off date will be analyzed and reported.

- The primary efficacy and selected safety analyses will also be performed for the following subgroups:
- Line of therapy (2^{nd} / 3^{rd}).

[redacted]

- 2nd line therapy: all patients who received only one line of prior antineoplastic therapy before the start of study treatment
- 3rd line therapy: all patients who received two lines of prior antineoplastic therapy before the start of study treatment (treatment with immune checkpoint inhibitor must have been the last treatment prior to study entry)

- Age category
- MSKCC and IMDC risk groups

Further details will be included in the Statistical Analysis Plan (SAP).

10.1 Analysis sets

10.1.1 Full Analysis Set

The FAS comprises all patients to whom study treatment has been assigned and who received at least one dose of pazopanib.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of pazopanib. The safety set and the FAS are the same for this single arm phase II study.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the protocol.

The protocol deviations **potentially** leading to exclusion from the PPS are:

- Diagnosis at screening different from histologically confirmed locally recurrent or metastatic predominantly clear cell renal cell carcinoma.
- No previous systemic therapy with an immune checkpoint inhibitor either as monotherapy or in combination therapy, or more than two previous line of anti-cancer systemic therapy.
- No measurable lesions at baseline.
- Another anti-neoplastic therapy administered after start of study treatment and prior to the first tumor assessment.

10.1.4 Other analysis sets

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for all patients in the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical at baseline will be summarized by system organ class and preferred term.

[redacted]

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety set will in general be used for the analyses of treatments. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure to pazopanib (expressed in months), the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the corresponding reasons will be summarized for the study treatment. All pazopanib dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system in the Safety set.

Anticancer therapies administered after the discontinuation of the study treatment will be listed and summarized according to the ATC classification system.

10.4 Primary objective

The primary objective of the study is to evaluate the efficacy of pazopanib as assessed by PFS based on local investigator assessment per RECIST v1.1 in patients with locally advanced/ metastatic RCC with predominantly clear cell component after previous therapy with immune checkpoint inhibitor treatment.

10.4.1 Variable

The primary efficacy variable of the study is PFS, defined as the time from the date of start of pazopanib treatment to the date of the first documented progression or death due to any cause. PFS will be assessed via local review according to RECIST 1.1 (see Appendix 2 for further details).

10.4.2 Statistical hypothesis, model, and method of analysis

No formal hypothesis will be tested in the study. An estimation of the median PFS with 95% confidence intervals will be provided in the FAS population. The Kaplan-Meier estimate of the PFS survival function will be estimated and displayed. The resulting median PFS time will be given with 95% confidence intervals, as well as 25th and 75th percentiles will be reported.

PFS probability at selected time-points (e.g., 3, 6 and 12 months) will also be estimated.

10.4.3 Handling of missing values/censoring/discontinuations

In the primary analysis, PFS will be censored at the date of the last adequate tumor assessment if no PFS event (disease progression or death due to any cause) is observed prior to the analysis cut-off date.

[redacted]

Only tumor assessments with a reported tumor response status of CR, PR or SD will be considered adequate to determine the censoring date.

If a PFS event is observed after two or more missing or non-adequate tumor assessments, then PFS will be censored at the last adequate tumor assessment before the PFS event. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of the event will be used.

10.4.4 Supportive and sensitivity analyses

As a supportive analysis, PFS may be analyzed based on the Per Protocol Set, using the same analysis conventions as in the primary efficacy analysis.

In addition, subgroup analysis by line of therapy subgroup (2^{nd}/ 3^{rd}), age category and MSKCC and IMDC risk groups will be performed in the FAS for PFS as appropriate. Details will be provided in the SAP.

10.5 Secondary objectives

The secondary efficacy and safety objectives that will be evaluated in the study include:

- ORR and CBR based on local investigator assessment as per RECIST 1.1
- OS
- DOR in the subset of patients with confirmed CR / PR;
- safety and tolerability
- PRO assessed by EQ-5D and FKSI-DRS questionnaires.

10.5.1 Key secondary objective(s)

Not applicable

10.5.2 Other secondary efficacy objectives

Overall response rate (ORR)

ORR is defined as the proportion of patients with best overall response (BOR) of CR or PR based on local investigator's assessment according to RECIST 1.1 (see Appendix 2 for details). Determination of BOR of PR or CR will be based on confirmed PR/CR as per RECIST 1.1.

ORR will be calculated based on the FAS and its exact 95% confidence interval (Clopper and Pearson 1934) will be presented.

Clinical benefit rate (CBR)

CBR is defined as the proportion of patients with a best overall response of confirmed CR, or PR or an overall lesion response of SD or Non-CR/Non-PD lasting ≥24 weeks based on local investigator's assessment according to RECIST 1.1.

CBR and its exact 95% confidence interval will be provided using FAS population.

[redacted]

Overall survival (OS)

OS is defined as the time from date of start of pazopanib treatment to date of death due to any cause. If a patient is not known to have died, then OS will be censored at the latest date the patient was known to be alive (on or before the cut-off date).

OS will be analyzed in the FAS population. The OS distribution will be estimated using the Kaplan-Meier method. The Kaplan-Meier curve will be graphically presented, and the median, 25th and 75th percentiles will be shown along with the corresponding 95% confidence intervals. OS probability at selected time-points (e.g., 6, 12 and 24 months) will also be estimated.

Duration of response (DOR)

DOR only applies to patients, whose best overall response is confirmed CR or PR, as per local investigator's assessment, according to RECIST 1.1. DOR is defined as the time from the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), to the date of the first documented progression or death due to underlying cancer, whichever comes first. In patients continuing without progression or death due to underlying cancer DOR will be censored at the date of their last adequate tumor assessment. DOR will be estimated using the Kaplan-Meier method. The median, 25th and 75th percentiles, and the corresponding 95% confidence intervals will be provided.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. Summary table and patient data listings will be used to analyze and present safety data.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication;
2. on-treatment including safety follow-up period: from day of first dose of study medication to 30 days after last dose of study medication;
3. post-treatment period: starting at day 31 after last dose of study medication.

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

For the safety evaluations (with the exception of AEs), the last available assessment performed on or before the date of study treatment start will be considered as the "baseline" assessment.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on NCI-CTCAE grades), relation to study treatment.

[redacted]

Serious adverse events, non-serious adverse events, adverse events of special interest (AESI) (see Section 8.1.3) and adverse events leading to study treatment discontinuation during the on-treatment period will be tabulated for safety set as well as by line of therapy subgroup (2^{nd}/ 3^{rd}), age category and MSKCC and IMDC risk groups.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

10.5.3.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. The calculation of NCI-CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

NCI-CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For laboratory tests where grades are not defined by NCI-CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

For laboratory tests where grades are defined by NCI-CTCAE v4.03:

- Worst post-baseline NCI-CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using NCI-CTCAE grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by NCI-CTCAE v4.03:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.
- Laboratory abnormalities will be summarized for safety set as well as by line of therapy subgroup (2^{nd}/ 3^{rd}), age and MSKCC and IDMC risk groups, as appropriate.

Listing of all laboratory data with values flagged to show the corresponding NCI-CTCAE v4.03 grade if applicable and the classifications relative to the laboratory normal ranges will be generated.

10.5.3.4 Other safety data

ECG

- Local 12-lead ECGs including HR, PR, QRS, QT, and QTcF intervals will be obtained for each subject at baseline, during the study treatment period and at the end of treatment. ECG data will be read and interpreted locally.
- The number and percentage of patients with notable ECG interval values and change from baseline ECG parameters by time point will be summarized in the Safety set.
- All collected data will be presented in data listings; notable values and abnormality finding will be flagged in the listing.

[redacted]

Echocardiogram/MUGA

- Local echocardiogram or MUGA will be obtained for each subject at baseline, during the study treatment period and at the end of treatment.
- Ejection fraction values will be classified based on NCI-CTCAE v4.03 and a shift table will be prepared for the Safety set to summarize the distribution of individual worst on-treatment values vs. the corresponding baseline values.
- All collected data will be presented in data listings and notable values will be flagged.

Vital signs

- Data on vital signs will be tabulated and listed, notable values will be flagged.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

Tolerability will be assessed by evaluating the incidence of drug-related adverse events by NCI-CTCAE grade and the incidence of events leading to study treatment discontinuation (see Section 10.5.3.2).

10.5.4 Resource utilization

Not applicable.

10.5.5 Patient-reported outcomes

The FAS will be used for analyzing the PRO data unless specified differently. The EQ-5D-5L and FSKI-DRS will be used to collect PRO data on the subject's health-related quality of life and disease-related symptoms.

The EQ-5D-5L is a general health status and health utility measure (Rabin 2001) and measures 5 dimension of health state: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression each assessed by a single question on a five-point ordinal scale EQ-5D Visual Analog Scale (VAS) is also included. The FKSI-Disease Related Symptoms (FKSI-DRS) is a 9-item questionnaire specifically designed to evaluate symptoms that are directly attributable to kidney cancer (Cella 2007) and includes patient's symptoms in the past seven days such as lack of energy, pain, bone-pain, shortness of breath, fatigue, blood in urine, etc. The scoring of these instruments will be done in accordance with the respective user's manual of the instrument.

Handling of missing data and generation of standard scores for the analysis will be performed in accordance with the respective scoring manual.

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be used to summarize the scored scales at each scheduled assessment time point. Additionally, changes from baseline in the scores at the time of each assessment will be descriptively analyzed. Additional statistical analyses such as repeated measures analysis for changes of the mean scores over time will be performed as appropriate. Patients with an evaluable baseline score and

[redacted]

at least one evaluable post baseline score during the treatment period will be included in the analysis of the changes from baseline. Summary tables and plots will be reported. All reported data will be presented in data listing.

[redacted]

[redacted]

[redacted]

10.7 Interim analysis

No formal interim analysis is planned for this trial.

10.8 Sample size calculation

Since there is no formal hypothesis testing, sample size for this study is not based on any statistical power consideration. A total of approximately 100 patients (with approximately 40 patients receiving pazopanib as 2nd-line therapy) are planned to be enrolled and treated in this study. In a retrospective study, Nadal et al. reported median PFS (mPFS) of 6.9 months (95% Cl: 3.7 to 10.1) in mRCC patients treated with VEGFR-TKI therapy after any PD-1combination (Nadal et al 2016). Based on this data, the median PFS for this patient population treated with pazopanib following prior treatment with immune checkpoint inhibitors is assumed to be approximately 6 months or less. Considering a recruitment period of 12 months and 6 months of follow up after LPFV, the expected 95% CIs for a median PFS for overall, 2nd line, and 3rd line patients with different sample sizes are presented in Table 10-1.

Table 10-1 Sample size and estimated 95% CI for median PFS

Patient population	Median PFS (months)	Sample size (N)	95% CI of median PFS (month)	Width (month)
Overall	5	90	3.96, 6.31	2.35
		100	4.01, 6.24	2.23
		110	4.05, 6.17	2.12

[redacted]

Patient population	Median PFS (months)	Sample size (N)	95% CI of median PFS (month)	Width (month)
2nd line	6	30	3.95, 9.12	5.18
		40	4.17, 8.62	4.45
		50	4.34, 8.30	3.96
3rd line	4	50	2.96, 5.40	2.44
		60	3.04, 5.26	2.22
		70	3.10, 5.16	2.05

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

[redacted]

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Male participants will be requested to provide an "Information for female partners of male study participants" form to female partners of child-bearing potential.

[redacted]

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g., www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

[redacted]

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

[redacted]

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g., UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

[redacted]

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[redacted]

14 Appendices

14.1 Appendix 1: Strong CYP3A4 inhibitors and inducers

Strong inhibitors of CYP3A4[1]	boceprevir, clarithromycin, conivaptan, grapefruit juice[2], indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, cobicistat, troleandomycin, danoprevir/ritonavir, eltegravir/ritonavir,

1. *A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by equal or more than 5-fold.*
2. *Effect* seems to be due to CYP2C19 inhibition by ethinyl estradiol

Strong inducers of CYP3A4[1]	avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort[5], rifabutin, phenobarbital, mitotane, enzalutamide
Moderate inducers of CYP3A4[2]	bosentan, efavirenz, etravirine, modafinil, nafcillin, ritonavir, thioridazine, tipranavir, semagacestat[4], talviraline[4], lopinavir, lersivirine
Weak inducers of CYP3A4[3]	amprenavir, aprepitant, armodafinil bexarotene, clobazam, danshen[5], dexamethasone, echinacea[5], gingko (ginkgo biloba)[5], glycyrrhizin[5], methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, pleconaril[4], primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, troglitazone[4], vinblastine, eslicarbazepine, ginseng[5], vemurafenib, boceprevir, sulfinpyrazone, ticagleror, vicriviroc/ritonavir, ritonavir, ticlopidine, brivacetam, Stribild (combo of elvitegravir, cobicistat, emtricitabine, and tenofovir)

1. A strong inducer for a specific CYP is defined as an inhibitor that decreases the AUC of a sensitive substrate for that CYP by equal or more than 80%
2. A moderate inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 50-80%.
3. A weak inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 20-50%.
4. Drugs not available in the US Market.
5. Herbal product

[redacted]

14.2 Appendix 2: Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1)

Document type:	TA Specific Guideline
Document status:	Version 3.2: February 11, 2016 Version 3.1: November 29, 2011 Version 3: October 19, 2009 Version 2: January 18, 2007 Version 1: December 13, 2002
Release date:	11-Feb-2016

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Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

[redacted]

1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 2 and the definition of best response in Section 3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

2.1 Definitions

2.1.1 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 3.2.8.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g., the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

[redacted]

- Cystic lesions:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g., longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g., in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 3.2.8.

2.2 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v.) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All screening/baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

[redacted]

- A change in methodology can be defined as either a change in contrast use (e.g., keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g., from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  - Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
  - Physical exams: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
  - Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
  - Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

[redacted]

- Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g., CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- **Cytology and histology:** Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination:** Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

2.3 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- Target lesions: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target:** Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g., clinical examination, photography) should be at least 10 mm in longest diameter. See Section 2.1.1.
- **Nodal target:** See Section 2.1.1.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions:** All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as

[redacted]

a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

2.4 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 2-1) and non-target lesions (Table 2-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 2-3) as well as the presence or absence of new lesions.

2.4.1 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

2.4.1.1 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

2.4.1.2 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given

[redacted]

for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

2.4.2 Determination of target lesion response

Table 2-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm [2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

1. SOD for CR may not be zero when nodal lesions are part of target lesions
2. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
3. In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 2.2).

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 2-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target

[redacted]

lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.

- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm

[redacted]

and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g., a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

2.4.3 Determination of non-target lesion response

Table 2-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.[2]

1. The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail.
2. It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).

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- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

2.4.4 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 2.2.

2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 2-3.

[redacted]

Table 2-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

1. This overall lesion response also applies when there are no non-target lesions identified at baseline.
2. Once confirmed PR was achieved, all these assessments are considered PR.
3. As defined in Section 2.4.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

3.1 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

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Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6 week tumor assessment frequency. However these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g., if the assessment occurs every 6 weeks with a time window of ± 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g., PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally

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disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Novartis calculated overall lesion response (based on measurements from Investigator)

The primary analysis of the best overall response will be based on the sequence of investigator/ calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize patients with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an

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unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g., populations based on an ITT approach).

3.2 Time to event variables

3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g., in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint.

3.2.2 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

3.2.4 PFS2

A recent EMA guidance (EMA 2012) recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses

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the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues w.r.t. censoring foreseen.

3.2.5 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

3.2.6 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates… If an

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inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

3.2.7 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

[redacted]

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

3.2.8 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g., X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 3.2.8).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.

[redacted]

- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

3.2.9 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g., in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 3-1.

Table 3-1 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 2.4.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g., in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which

[redacted]

exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

3.2.10 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics-April 2005) as a reference, the following analyses can be considered:

[redacted]

Table 3-2 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

1. =Definitions can be found in Section 3.2.7.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 3.2.7.
3. =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

[redacted]

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g., CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g., radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g., by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 3-2 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

[redacted]

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g., on incomplete dates).

4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Patient/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

Death is a reason which "**must**" lead to discontinuation of patient from trial.

[redacted]

4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Patient/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

[redacted]

4.5 Programming rules

The following should be used for programming of efficacy results:

4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

4.5.2 Incomplete assessment dates

All investigation dates (e.g., X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 3.2.7). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

[redacted]

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 3-2)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g., reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g., withdrawal of consent, lost to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

[redacted]

5 References (available upon request)

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