CLINICAL TRIAL PROTOCOL

TITLE:

A Phase II Study of Propranolol Plus Sunitinib in First-line Treatment of Metastatic Renal Cell Carcinoma (ProSun Study)

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DEVELOPMENT PHASE

2

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List of Abbreviations

AC - adenyl cyclase
AE - adverse event
ALP - alkaline phosphatase
ALT - alanine transaminase
ANA - antinuclear antibodies
ANOVA - analysis of variance
AP-1 - activator protein 1
APTT - activated partial thromboplastin time
AST - aspartate aminotransferase
AV - atrioventricular
BAD - BCL2-associated death protein
cAMP - cyclic 3'–5' adenosine monophosphate
ccRCC - clear-cell renal cell carcinoma
CI - confidence Interval
COX - cyclooxygenase
CR - complete response
CRF - Case Report Form
CREB/ATF - cAMP response element binding protein/activating transcription factor
crRCC - chromophobe renal cell carcinoma
CSF-1R - colony stimulating factor 1 receptor
CT - computed tomography
CTLA-4 - cytotoxic T-lymphocyte-associated antigen 4
CYP - cytochrome P
D - day
DCR - disease control rate
DRS - disease-related stress
E - epinephrine
ECG - electrocardiography
EGF - epidermal growth factor
ELISA - enzyme-linked immunosorbent assay
EMA - European Medical Agency
EMT - epithelial-mesenchymal transition
EORTC - European Organisation for Research and Treatment of Cancer
EPAC - exchange protein activated by adenylyl cyclase
EPO - erythropoietin
ERK - extracellular signal-regulated kinase
FAK - focal adhesion kinase
FDA - Food and Drug Administration
FGF - fibroblast growth factor
FGFR - fibroblast growth factor receptor
FKSI-15 - FACT-Kidney Symptom Index - 15

FLT-3 - fms-related tyrosine kinase 3
GCP - Good Clinical Practice
HER-2 - human epidermal growth factor receptor 2
HGF - hepatocyte growth factor
HIF - hypoxia-inducible factor
HIV - human immunodeficiency virus
HLQoL - health related quality of life
HLRCC - hereditary leiomyomatosis and renal cell cancer
HR - hazard ratio
IFN-α - Interferon alpha
IH - infantile haemangioma
IL - interleukin
INR - international normalized ratio
IRB - Institutional Review Board
IV - intravenous
KIT - v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
LMWH - low molecular weight heparin
MAPK - mitogen-activated protein kinase
MEK - mitogen-activated protein kinase kinase
MMP - matrix metalloproteinase
MRI - magnetic resonance imaging
MSKCC - Memorial Sloan-Kettering Cancer Center
mTOR - mammalian target of rapamycin
MU - million units
NA - not applicable
NE - norepinephrine
NFκB - nuclear factor kappa B
NK - natural killer
OS - overall survival
PD - progressive disease
PD-1 - programmed death-1
PDGF - platelet-derived growth factor
PDGFR - platelet-derived growth factor receptor
PET - positron emission tomography
PFS - progression-free survival
PI3K - phosphoinositide 3-kinase
PKA - protein kinase A
PSS - Perceived Stress Scale
PR - partial response
pRCC - papillary enal cell carcinoma
QoL - quality of life
RANKL - receptor activator of nuclear factor kappa-B ligand
RCC - renal cell carcinoma
RECIST - Response Evaluation Criteria in Solid Tumors

RET - rearranged during transfection proto-oncogene
SAE - serious adverse event
SD - stable disease
SDH - succinate-dehydrogenase
SICF - Subject Information and Consent Form
SoD - sum of the diameters
SNAI2 - snail family transcriptional repressor 2
SNS - sympathetic nervous system
STAT-3 - signal transducer and activator of transcription-3
TGFα - transforming growth factor alpha
TKI - tyrosine kinase inhibitor
TNFα - tumour necrosis factor alpha
TPR - time point response
TSH - thyroid-stimulating hormone
UE - unable to evaluate
VEGF - vascular endothelial growth factor
VEGFR - vascular endothelial growth factor receptor
vHL - von Hippel-Lindau
W - week

Statement of Compliance

I ensure that the trial will be conducted in compliance with the protocol and with Good Clinical Practice (GCP).

I ensure that no deviation from, or changes to the protocol will take place without prior agreement from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

I ensure the trial will be registered on the www.clinicaltrials.gov website and wherever appropriate.

I ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

Paweł Chrom

Print/Type Name

_____

Signed:

Date (DD/MM/YYYY): 10/09/2017

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Clinical Trial Summary

TITLE	A Phase II Study of Propranolol Plus Sunitinib in First-line Treatment of Metastatic Renal Cell Carcinoma (ProSun Study)
PRINCIPAL INVESTIGATOR	Pawel Chrom, M.D.
TRIAL LOCATION	Military Institute of Medicine Szaserów 128, 04-141 Warsaw, Poland
STUDY OBJECTIVES	**Primary objective:** To assess an effectiveness of therapy with propranolol plus sunitinib in terms of objective response rate in patients with metastatic renal cell carcinoma. **Secondary objectives:** To assess the following outcomes: overall survival, progression-free survival, disease control rate, incidence and severity of adverse events, changes from baseline in vital signs and laboratory results, health-related quality of life, disease-related stress, characterization of relationship between the primary tumour tissue and serum biomarkers with treatment and clinical outcomes.
STUDY DESIGN	It is a single-arm, single-center, open-label, phase II study. Eligible patients will be included in the single investigational cohort treated with: - oral sunitinib at a starting dose of 50 mg once daily in 6-weeks cycles consisting of 4 weeks of treatment followed by 2 weeks off the drug, - oral propranolol at a starting dose of 40 mg two times daily to a maximum dose of 240 mg a day Physical examination, laboratory findings, electrocardiography and filling health-related quality of life and disease-related stress questionnaires will take place every 6 weeks; computed tomography/magnetic resonance imaging scan will be performed every 12 weeks. The study treatment will last until disease progression, unacceptable toxicity or withdrawal of consent. Each patient will have a summary visit at the time of discontinuation from study treatment. The postdiscontinuation period will continue until death or the end of study data collection.
STUDY POPULATION **Main inclusion criteria:**	1. Histological diagnosis of clear-cell renal cell carcinoma or mixed-type renal cell carcinoma with more than 60% of clear-cell component in the primary tumor. 2. Diagnosis of stage IV renal cell carcinoma (primary metastatic or recurrence after surgical procedure). 3. Prior nephrectomy (complete or partial). 4. Presence of measurable disease. 5. Karnofsky performance status: 80-100%. 6. Favorable or intermediate risk according to Memorial Sloan-

	Kettering Cancer Center Score. 7. Adequate organ function, including the following: - hepatic: total bilirubin ≤ 2 times the upper limit of normal (excluding patients with Gilbert syndrome), AST and ALT ≤ 5 times the upper limit of normal, - renal: serum creatinine ≤ 2 times the upper limit of normal, - bone marrow: absolute neutrophil count ≥ 1500/mm^3, platelets ≥ 100000/mm^3, hemoglobin ≥ 9,5 g/dl. 8. Normal thyroid function (natural or with supplementation of thyroid hormones). 9. Age ≥ 18 years. 10. Written informed consent prior to study entry.
Main exclusion criteria:	1. Prior systemic therapy of renal cell carcinoma. 2. Treatment with propranolol within 6 months of study entry. 3. Metastases in the central nervous system (patients who had brain metastases that were surgically resected or treated with radiotherapy in the past and now are without neurological symptoms, are allowed on protocol). 4. Female patients who are pregnant or breast feeding. 5. Presence of other malignancies (patients with carcinoma in situ of the cervix or basal cell carcinoma of the skin are allowed on protocol). 6. Presence of any severe and/or uncontrolled medical conditions. 7. Presence of any contraindication to propranolol.
Expected number of patients:	33
INVESTIGATIONAL PRODUCTS **Formulations:**	Tablets for oral administration, containing: - sunitinib: 50 mg, 37,5 mg, 25 mg, or 12,5 mg: - propranolol: 40 mg
STATISTICAL CONSIDERATIONS	The optimal two-stage Simon design. Under the conditions of: α level of 0.050, β level of 0.200, the increase in objective response rate from 0.30 for sunitinib monotherapy to 0.55 for propranolol plus sunitinib combination, a minimum of 15 patients will be included in the first stage. The trial will be terminated if 6 or fewer patients achieve objective response rate. If the trial goes on to the second stage, a total of 33 patients will be studied. If the total number of patients achieving objective response rate is less than or equal to 13, the combination is rejected.

1. Background

1.1 Renal Cell Carcinoma

1.1.1 Epidemiology

Kidney cancer accounts for approximately 2-3% of adult malignancies with 337860 new cases and 143406 deaths worldwide [1]. The American Cancer Society estimates that there will be 62700 new cases (39650 in males, 23050 in females) of malignant tumors of the kidney, with 14240 deaths (9240 in males, 5000 in females) in United States in 2016. The most common type of kidney cancer - renal cell carcinoma (RCC) – is expected to account for 80-90% of this incidence and mortality [2].

RCC is more common in populations of Northern Europe and North America than in those of other parts of the world. It is diagnosed more often in men than in women (1,6:1) and with blacks than in whites in United States. The patient's median age at the time of diagnosis was 64 years, according to a 4-year observation (2010-2014) [3]. Newly diagnosed patients with a metastatic disease (stage IV, according to TNM Classification of Malignant Tumors) accounted for 16% during the period of 2007-2013. The 5-year survival rate in that group was 11.7 % [3].

1.1.2 The Role of VHL-HIF Axis in the Pathogenesis of RCC

The most frequent histological subtypes of RCC include clear-cell RCC (ccRCC), papillary RCC (pRCC), and chromophobe RCC (crRCC) that together represent more than 90% of all RCCs [4].

The knowledge of the genetic basis of RCC starts more than 100 years ago with reports of Collins, von Hippel and Lindau, who observed vascular-appearing growths involving the retina and occurring in a familial context [5-7]. The disease the researchers referred to was an autosomal-dominant dominant condition predisposing carriers to the development of hemangioblastomas, pheochromocytomas as well as RCCs, named further the von Hippel-Lindau disease (vHL). The sequencing of human von Hippel-Lindau gene (*VHL*) in 1993 was a mile-step in understanding the molecular basis of RCC [8]. Its germline inactivating mutation causes vHL disease [9]. The gene, mapped to 3p25, contains three exons and encodes 2 proteins by virtue of 2 alternative, start codons. Both forms are referred to as "pVHL" because they behave similarly in biochemical and biological aspects, as well as *VHL* mutations in RCC affect both pVHL isoforms [10]. pVHL is the substrate recognition component of an E3 ubiquitin ligase complex that facilitates the oxygen-dependent ubiquitnation of the hypoxia-inducible factors (HIFs). HIF is a heterodimeric DNA-binding transcription factor consisting of an unstable α subunit and a stable β subunit. It regulates the expression of more than 1,000 target genes through binding to hypoxia response elements. The target genes include those encoding vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor alpha (TGFα), erythropoietin (EPO), cyclin D, hepatocyte growth factor (HGF), interleukin-6 (IL-6) and mammalian target of rapamycin (mTOR). Additionally, HIF upregulates the nuclear factor kappa B (NFκB) which is a transcription factor that contributes to ccRCC development and may be responsible for resistance of the tumour to many forms of therapy [11]. pVHL also inhibits a pro-carcinogenic Wnt/β-catenin pathway by promoting the ubiquitination of the Wnt signaling protein Disheveled [12]. In the presence of normal oxygen tension in the tissue

microenvironment, the HIFα subunits are recognized by pVHL, polyubiquitinated, and then destroyed by the proteasome. Under low oxygen conditions or in the absence of functional pVHL, the α subunit is stabilized and dimerizes with a β subunit. Further, HIF heterodimer accumulates within the cytoplasm, translocates to the nucleus where targets hypoxia responsive genes. Using this pathway, HIF is involved in numerous processes, including cell proliferation, angiogenesis, extracellular matrix degradation, vascular tone, and erythropoiesis - all the processes involved in cancer development. Therefore, when *VHL* gene performs in a normal pattern, it acts as a tumour-supressor [13, 14].

One of the recent studies reported the prevalence of VHL loss in ccRCC to be as high as 91%. *VHL* mutation occurred in 83.4% of cases, whereas methylation of multiple promoter sites inactivating *VHL* was observed in another 8.3% of cases, none containing *VHL* mutations [15]. Multiple studies showed that *VHL* loss occurred early in the development of ccRCC. The intratumoural heterogeneity of ccRCC and the discovery of differential HIFα expression patterns in pVHL-defective ccRCC results in suspicion that VHL loss may set the stage for a branched evolution of tumorigenesis in which HIF family members can become deregulated in different ways, leading to varying phenotypes of disease [16].

1.1.3 The Role of Beta-adrenergic Receptors in Carcinogenesis

Sympathetic nervous system (SNS) that innervates every major organ system of the body is responsible for fight-or-flight stress responses. Due to physiological, psychological, and environmental threats to homeostasis it releases catecholamine neurotransmitters: norepinephrine (NE) via neural junctions and epinephrine (E) from chromaffin cells of the adrenal medulla into circulating blood. Seconds after an acute stress-evoking event NE and E levels may increase by more than 10-fold. However, basal levels also slightly vary over time and differ in solid tissues versus blood [17]. NE and E act via α1, α2, β1, β2, and β3 receptors which are distributed distinctly across different types of tissues where are responsible for numerous physiological processes. The activation of the β1 receptor include increased cardiac output, renin release from juxtaglomerular cells of the kidney, increased ghrelin form the stomach. The activation of the β2 receptor results in actions such as smooth muscle relaxation in bronchi, gastrointestinal tract, and vessels, anabolism in skeletal muscles, insulin secretion, glycogenolysis, whereas the β3 receptor is responsible for lipolysis in adipose tissue. Binding NE and E to β receptors stimulates adenyl cyclase (AC) to synthesize cyclic 3'–5' adenosine monophosphate (cAMP). cAMP regulates multiple cellular processes via two major pathways. The first pathway is based on activation of protein kinase A (PKA) that phosphorylates serine or threonine residues on target proteins. The regulation of cellular processes via PKA includes metabolism, differentiation, morphology, motility, secretion, neurotransmission, and gene transcription. The effect on gene expression is mediated by PKA-induced phosphorylation of the cAMP response element binding protein/activating transcription factor (CREB/ATF) family. These transcription factors engage approximately 20% of human genes [18, 19]. The second, PKA-independent pathway uses the guanine nucleotide exchange protein activated by adenylyl cyclase (EPAC) activates the Ras-like guanine triphosphatase Rap1A that results in stimulation of mitogen-activated protein kinase pathway (MAPK). The effect of this stimulation is an engagement of downstream effectors such as B-Raf kinase, mitogen-activated protein kinase kinase (MEK) 1/2, and extracellular signal-regulated kinases (ERK) 1/2. All these factors play important role in cell growth, proliferation, morphology, motility, and secretion dynamics [20].

In the preclinical studies, activation of β-adrenergic receptors by stress hormones has been found to play significant role in tumour progression. The AC-cAMP-PKA pathway enables phosphorylation of CREB that induces the transcription of genes encoding numerous factors responsible for angiogenesis (VEGF), tissue invasion (matrix metalloproteinases [MMPs] 2/9), and inflammation (IL-6, IL-8). The cAMP/PKA/phosphoinositide 3-kinase (PI3K)/Akt/mTOR/p70S6 kinase stimulates *VEGF* expression dependent on HIF1α [21-24]. The PKA-independent pathway was reported to induce NFκB and activator protein 1 (AP-1) that regulate the translation of VEGF, MMPs and interleukins [25]. The stimulation of β2-adrenoceptors activates actin-related proto-oncogene tyrosine-protein kinase Src and subsequently phosphorylation of focal adhesion kinase (FAK) that results in lower level of anoikis [26]. Furthermore, β2-adrenoceptor stimulation by adrenaline leads to PKA-dependent BCL2-associated death protein (BAD) phosphorylation which results in resistance to chemotherapy-induced apoptosis [27]. The activation of PKA-dependent pathway by NE results in Src and signal transducer and activator of transcription-3 (STAT-3) stimulation that may drive the growth, invasion and metastasis process in ovarian cancer [28, 29]. On the other hand, a metastatic switch may be triggered by the tumour-infiltrating macrophages that produce various pro-metastatic factors after stress hormones release [30]. The β-adrenergic signaling may also inhibit p53-mediated DNA repair [31], suppress cytotoxic T lymphocyte and natural killer (NK) cell responses [32], inhibit expression of interferons [33], upregulate the human epidermal growth factor receptor 2 (HER2) signaling pathway [34] and induce the snail family transcriptional repressor 2 (SNAI2) which regulates the epithelial-mesenchymal transition (EMT) [35].

Theoretically, the β-adrenergic tumour growth might be driven via circulating catecholamines or via NE local release from SNS nerve fibers. Recent studies, however, suggest that the second option is most possible. In ovarian cancer tissues E is not detectable and concomitantly NE levels are higher than those in circulating blood. What is more, intratumour NE levels correlate with patient psychosocial risk factors and with tumor gene expression profiles, whereas NE and E blood levels do not [36, 37]. Human breast and ovarian cancer tissues are extensively innervated by peri-vascular fibers that may supply tumour and stromal cells with NE [30, 38]. It was also found that social stress enhances sympathetic innervation of primate lymph nodes [39] and similar phenomenon in tumour tissues cannot be excluded.

1.1.4 The Place of Sunitinib in Treatment of Metastatic RCC

Surgical resection remains the only known effective treatment for localized renal cell carcinoma, but it also is used for palliation in metastatic disease. Clinical studies showed that nephrectomy increases effectiveness of further systemic therapies [40, 41]. Moreover, if the metastases are singular and resectable, metastasectomy should be also performed. Resection of single metastases from lung, brain or liver can provide a long time without starting a systemic treatment [42, 43].

For decades, treatment with classic chemotherapy was unsuccessful in patients with metastatic disease. Interleukin-2 (Il-2) and Interferon alpha (IFN-α) introduced in 1990s were the first drugs that were able to evoke dramatic and durable tumor regression, however in small percentage of patients with significant toxic side effects [44]. Sequencing of human *VHL* (von Hippel-Lindau) gene and the discovery that its abnormalities are found in majority of clear-cell RCC cases were a mile-step in development of active agents. Currently, they include VEGFR-targeted tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib, axitinib, lenvatinib and cabozantinib), VEGF antibody (bevacizumab),

mTOR pathway inhibitors (temsirolimus and everolimus) and programmed death-1 (PD-1) antibody (nivolumab) [45]. All these agents demonstrated clinical benefit in many investigational studies and have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Sunitinib is an orally administrated drug that was approved by FDA in 2005. It is an inhibitor of platelet-derived growth factor receptor (PDGFR) -α, -β, vascular endothelial growth factor receptor (VEGFR) -1, -2, -3, KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog), FLT-3 (fms-related tyrosine kinase 3), CSF-1R (colony stimulating factor 1 receptor) and rearranged during transfection (RET) proto-oncogene. In a large phase III registration study (NCT00098657) sunitinib was superior in efficacy when compared to IFN-α in the control arm. There were 750 previously untreated patients with metastatic disease enrolled into the trial, with randomization ratio 1:1 in both arms. Patients in investigational arm received sunitinib at a dose of 50 mg daily for four weeks, then two weeks without medication (a six-week cycle). In control arm IFN-α was given as a subcutaneous injection three times per week on nonconsecutive days at 3 million units (MU) per dose during the first week, 6 MU per dose the second week, and 9 MU per dose thereafter. A dose reduction was allowed due to severe or uncontrolled adverse effects (to 37.5 mg and then to 25 mg daily for sunitinib, and to 6 MU and then to 3 MU three times per week for IFN-α). Median progression-free survival (PFS) was 11.0 months for sunitinib vs 5.0 months for IFN-α (Hazard Ratio [HR]=0.42, 95% Confidence Interval [CI]: 0.32-0.54, p<0.001). Median overall survival (OS) was 24.6 vs. 21.8 (HR=0.821, 95% CI: 0.673-1.001, p=0.051) and objective response rate (ORR) was 31% (95% CI: 26 to 36) vs. 6% (95% CI: 4% to 9%) for sunitinib and IFN-α, respectively. All-grade adverse events occurred more frequently in the sunitinib group than in the IFN-α group. Patients in the sunitinib group, as compared with those in the IFN-α group, had higher rates of grade 3 diarrhea (5% vs. no cases), vomiting (4% vs. 1%), hypertension (8% vs. 1%), and the hand–foot syndrome (5% vs. no cases, p<0.05 for all comparisons). Treatment-related grade 3 or 4 fatigue was significantly higher among patients in the IFN-α group than in the sunitinib group (12% vs. 7%, p<0.05). Grade 3 or 4 leukopenia, neutropenia, and thrombocytopenia occurred more often in the sunitinib group than in the IFN-α group (p<0.05 for all comparisons) [46]. In a retrospective, population-based analysis, efficacy of sunitinib was similar as in the registration study. Based on data of 6159 sunitinib-treated patients, median OS was 22.3 months (95% CI: 21.4-23.2), whereas median PFS was 8.4 months (95% CI 8.2-8.7). Response to sunitinib therapy was assessed in 5561 patients of whom 1687 (30%) achieved complete response (CR) or partial response (PR) [47]. Recent retrospective analysis of Bracarda et al. showed improved safety profile of patients who moved to a modified 2/1 schedule of sunitinib compared with that observed during the initial 4/2 schedule, without sacrifice the efficacy [48]. In a randomized phase II study of Lee et al., sunitinib administered with a 2/1 schedule was associated with less toxicity and higher 6-month failure-free survival than a 4/2 schedule, without compromising the efficacy in terms of ORR and time-to-progression [49].

1.2 Propranolol

1.2.1 Pharmacology

Propranolol (1-naphthalen-1-yloxy-3-(propan-2-ylamino)propan-2-ol), firstly developed in the 1960s, is a non-cardioselective sympatholytic β-adrenergic blocker with a similar binding affinity for β1- and

β2- and a much lower affinity (approximately 100-fold) for the β3-adrenoreceptor [50]. It possesses no other autonomic nervous system activity. After complete β-adrenoreceptor blockage, the NE release in synapsis may only result in α-adrenoceptor activation, and thus propranolol is considered as a weak indirect α-adrenoceptor agonist [51]. At dosages greater than required for β blockade it presents with strong membrane stabilizing activity. There is also an evidence that propranolol may function as an antagonist of 5-HT_{1A} and 5-HT_{1B} serotonin receptors [52].

After oral intake, propranolol undergoes rapid absorption in the intestine. It is highly lipophilic and more than 90% bound with plasma proteins. Peak plasma concentrations occur about 1 to 4 hours after an oral dose. Plasma half-life is 3 to 6 hours following single dose or 10 hours for extended release tablets. Mean peak plasma concentration following a single oral dose of 40 mg and 160 mg is 38 ng/ml and 200-245 ng/ml, respectively. The extended release tablets result in a peak of 18-50 ng/ml. Bioavailability after oral administration is within the range of 25-35% due to extensive first-pass hepatic clearance and may be increased up by 50% during concomitant food intake with no further change in time to peak concentration, plasma binding, half-life, or the amount of unchanged drug in the urine. Propranolol crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Its volume of distribution is approximately 4 liters/kg. The metabolism of propranolol takes place mainly in the liver and involves cytochromes P (CYPs) CYP2D6, CYP1A2 and CYP2C19. Propranolol is also a substrate for the intestinal efflux transporter, p-glycoprotein. Excretion is primarily renal, but about 1-4% of a dose is found in the faeces as unchanged drug and metabolites. Propranolol plasma clearance is reduced in elderly and Caucasians, as well as in patients with chronic renal failure and cirrhosis. Blood levels of propranolol may be increased by co-administration with substrates or inhibitors of CYP2D6 (i.e. amiodarone, cimetidine, delavudin, fluoxetine, paroxetine, quinidine, and ritonavir), CYP1A2 (i.e. imipramine, cimetidine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline, zileuton, zolmitriptan, and rizatriptan), and CYP2C19 (i.e. fluconazole, cimetidine, fluoxetine, fluvoxamine, tenioposide, and tolbutamide). Blood levels of propranolol may be decreased by co-administration with CYP inducers such as rifampin, ethanol, phenytoin, phenobarbital and cigarette smoking. Propranolol is not significantly dialyzable [53-56].

1.2.2 Current Indications and Dosing

Currently, propranolol is used in the treatment of hypertension, angina pectoris, cardiac dysrhythmias, tachycardia, anxiety, thyrotoxicosis, infantile hemangiomas (IH), and essential tremor. It is used in prophylaxis of migraine and upper gastrointestinal tract bleeding in patients with portal hypertension as well as for the long term prevention of sudden cardiac death in patients who have shown evidence of dysrhythmias during the acute phase of myocardial infarction.

Usually, the initial propranolol dose in adults is 40 mg two or three times daily and may be increased by the same amount at weekly intervals to a maximum daily dose of 320 mg (immediate-release tablets). If it is necessary to withdraw propranolol, this should be done gradually, or another β-adrenergic receptor blocker should be substituted [53, 57].

1.2.3 Antineoplastic Potential

Pre-clinical studies revealed wide antineoplastic potential of propranolol that includes inhibiton of proliferation, migration, invasion and angiogenesis, as well as induction of apoptosis, treatment sensitization and immunomodulation. Propranolol decreased proliferation rate associated with

catecholamines or isoproterenol in colorectal, pancreatic and lung adenocarcinoma cancer cells [58-60]. In oral squamous cell carcinoma cells proliferation was induced via β2 signalling pathway activated by IL-6 after stimulation of NE and isoproterenol. Then the proliferation rate was inhibited by IL-6 specific antibody and propranolol [61]. Similarly, a decreased level of IL-6 concomitantly with inhibition of metastatic growth was reported in a murine melanoma model after propranolol treatment [62]. Propranolol was more potent in reducing the proliferation, migration, and invasion of non-stimulated breast, colon, and hepatocellular cancer cells than the selective β1 receptor agonist, atenolol [63]. Propranolol inhibited the NE-induced upregulation of MMP-2 and MMP-9 which are responsible for tissue remodeling process. This resulted in decreased tumour invasion of breast cancer, ovarian cancer, nasopharyngeal carcinoma, pancreatic cancer, gastric adenocarcinoma, melanoma, prostate cancer and IH [64-71]. NE induces EMT via TGF-β-adrenoreceptor pathway that leads to increased metastatic potential and this effect was shown to be inhibited in colorectal cancer cell lines by propranolol [72]. In breast cancer cell lines, isoproterenol reduced Rap1-dependent cell-cell adhesion and promoted cell migration, whereas propranolol reduced the level of migration [73]. Catecholamine signaling was also reported to increase breast cancer cell colonization of bone via upregulation of receptor activator of nuclear factor kappa-B ligand (RANKL), which was reversed by propranolol or the RANKL inhibitor denosumab [74]. Propranolol induced cell cycle arrest and apoptosis in gastric carcinoma cell lines that was associated with a decrease of NF-κB, VEGF, cyclooxygenase (COX) 2, MMP-2 and MMP-9 expression [68]. The pro-apoptotic effect of propranolol was observed in head and neck squamous cell carcinoma and neuroblastoma cell lines and was connected to increased expression of p53 and p73 proteins [75, 76]. In another study on hemangioblastoma cells from vHL patients, propranolol decreased the viability and increased apoptosis that was associated with a decreased the expression of HIF protein and its target genes [77]. In ovarian cancer cell lines, propranolol blocked the angiogenesis by decreasing the VEGF expression which was previously stimulated by β-adrenergic agonists. Catecholamine induction of PKA-dependent signaling pathway was identified as a major mechanism by which behavioural stress enhanced tumour angiogenesis [78]. Propranolol inhibited brain endothelial cells tubulogenesis and matrix MMP-9 secretion in human glioblastoma [79]. HIF-1α expression was reported to be upregulated by NE, via the cAMP/PKA/Akt/p70S6K pathway, whereas propranolol completely abolished induction of VEGF expression and HIF-1α protein amount by NE and resulted in decreased angiogenesis in various cancer cell lines [80]. Propranolol also exhibited a potential to revert drug resistance of some leukemia cell lines to doxorubicin and revealed synergistic role with paclitaxel and 5-fluorouracil in number of human cancer and non-cancer cell lines [81, 82]. Catecholamines were reported to reduce NK cell and cytotoxic T lymphocyte numbers as well as tumour necrosis factor alpha (TNFα) and IFN-γ levels and this could be reversed by propranolol [83-85].

A positive effect of propranolol on cancer has been observed in epidemiological studies that assessed hypertensive and non-hypertensive patients. The study of Chang et al. compared 12119 patients treated with propranolol for more than 6 months to 12119 non-propranolol users over a 12 year period. Overall, the incidence for developing cancer was lower in the propranolol cohort (HR: 0.75; 95% CI: 0.67-0.85; p<0.001). Site specific analysis showed a decreased risk in head and neck cancers (HR=0.58; 95% CI: 0.35-0.95), oesophagus (HR=0.35; 95% CI: 0.13-0.96), stomach (HR=0.54; 95% CI: 0.30-0.98), colon (HR=0.68; 95% CI: 0.49-0.93), and prostate cancers (HR=0.52; 95% CI: 0.33-0.83) [86]. The study of Nkontchou showed that the use of propranolol in patients with cirrhosis due to

hepatitis C was associated with a decreased risk of hepatocellular carcinoma (HR=0.25; 95% CI: 0.09-0.65; p=0.004) [87]. In the study of Barron et al. women treated with propranolol (n=70) or atenolol (n=525) in the year prior to breast cancer diagnosis were matched with women not receiving β-blocker treatment (n=4738). Patients in the propranolol group had lower risk of having T4 (odds ratio [OR]=0.24, 95% CI: 0.07-0.85) or N2/N3/M1 (OR=0.20; 95% CI: 0.04-0.88) tumor compared with matched non-users. The cumulative probability of breast cancer-specific mortality was significantly lower for propranolol users compared with matched nonusers (HR=0.19; 95% CI: 0.06-0.60). There was no difference in T4 or N2/N3/M1 tumor incidence or breast cancer-specific mortality between atenolol users and matched non-users [88].

Propranolol was also assessed in small interventional studies. In a series of seven cases of advanced angiosarcoma, propranolol (40 mg twice daily) was combined with weekly vinblastine (intravenous [IV] 6 mg/m^2 to a maximum of 10 mg) and methotrexate (35 mg/m^2 to a maximum of 50 mg) for up to 12 months followed by maintenance of propranolol (40 mg twice daily), oral etoposide (50 mg/day) and oral cyclophosphamide (50 mg/day) for 20 consecutive days in cycles of 30 days. The treatment was well tolerated and resulted in ORR of 100%. Median PFS and OS were 11 months (range 5-24) and 16 months (range 10-30), respectively [89]. A combination of propranolol (20 mg twice daily, then titrated to maintain heart rate around 80 per minute) plus etodolac (400 mg twice daily) with metronomic temozolomide was compared to temozolomide monotherapy in 32 patients with recurrent glioblastoma. Patients treated with combination therapy had greater median time to progression (8.8 months versus 5.2 months), 6-months survival rate (63% versus 40%) and 1-year survival rate (22% versus 12%) than those treated with temozolomide monotherapy, respectively [90]. The same combination of propranolol and etodolac was tested with concomitant nab-paclitaxel plus gemcitabine in advanced pancreatic cancer. Patients randomized to four-drug therapy had greater PFS (11.8 months versus 7.2 months) and OS (15.9 months versus 10.5 months) than those receiving standard two-drug, respectively. Additionally, patients receiving propranolol plus etodolac experienced reduced pain and neuropathy and increased weight gain [91]. As a β-blocker, propranolol may also reduce the level of emotional distress, measured in terms of the number and rate of intrusive thoughts, associated with a cancer diagnosis [92].

1.2.4 Safety Results

Propranolol is generally a well tolerated drug. Its adverse effects are listed in Section 7.2.2. The initiation of propranolol may lead to initial adverse effects which may resolve during dose titration to a maintenance dose. Sudden termination of treatment is not advised. The dose should be tapered rather than stopped abruptly. There are no reports of increased toxicity of propranolol in patients with cancer likewise during combining propranolol with other antineoplastic agents mentioned in Section 1.2.3.

Because sunitinib can prolong the PR interval of the electrocardiogram in some patients, theoretically, its coadministration with propranolol, which also prolongs the PR interval, may result in increased risk of conduction disturbances and atrioventricular block. Thus, caution is advised if sunitinib is used concomitantly with propranolol, especially in the elderly and patients with known conduction problems (e.g., marked first-degree atrioventricular [AV] block; second-degree or higher AV block; sick sinus syndrome without pacemaker) or severe cardiac disease such as myocardial ischemia or heart failure. Despite the presence of sunitinib for more than 10 years in clinical practice,

no serious cardiac and other type toxicity was reported for coadministration of sunitinib and propranolol.

1.3 Study Rationale

Nowadays, first-line treatment with sunitinib is standard of care in patients with metastatic RCC who are classified into favourable- or intermediate-risk group according to Memorial Sloan-Kettering Cancer Center (MSKCC) criteria. However, disease progression occurs in most cases as cancer cells are primary or secondary resistant to sunitinib. Therefore, new strategies are needed to provide an improved option with maximal curative potential. New therapeutic approaches include combining sunitinib with autologous dendritic cell immunotherapy, AGS-003 (NCT01582672), PD-L1 inhibitor atezolizumab with VEGF inhibitor bevacizumab (NCT02420821), PD-L1 inhibitor avelumab with VEGFR inhibitor axitinib (NCT02684006), VEGFR/fibroblast growth factor receptor (FGFR) inhibitor lenvatinib with PD-1 inhibitor pembrolizumab (NCT02811861), and dual checkpoint inhibition: PD-1 inhibitor nivolumab with cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor ipilimumab (NCT02231749).

Other directions in development of improved treatment options in metastatic RCC are focused on drugs available on the market for years that are prescribed primarily for non-malignant diseases. Their antitumor activity was confirmed in preclinical studies and now they are being investigated in clinical trials. These studies include dalteparin, a low molecular weight heparin (LMWH) in combination with sunitinib in first-lline setting (NCT01061411); prednisone, a glucocorticoid, in combination with everolimus in VEGFR pre-treated patients (NCT02479490); hydroxychloroquine, antimalaric drug, in combination with IL-2 (NCT01550367); metformin, an anti-diabetic biguanide, in combination with vandetanib in hereditary leiomyomatosis and renal cell cancer (HLRCC), succinate-dehydrogenase (SDH) mutation-associated RCC (SDH-RCC) or sporadic papillary RCC (NCT02495103); a monotherapy with low dose naltrexone, an opioid antagonist, for metastatic melanoma, castrate resistant prostate cancer or RCC (NCT01650350).

Since 1960s, propranolol is used worldwide in different indications, mostly for treatment of cardiovascular diseases. Despite numerous pre-clinical and clinical studies that described its antineoplastic potential, it was not studied extensively as a pure anti-cancer agent in RCC. In the current clinical practice, its anti-tumour activity is limited to benign tumour - IH. Due to favourable toxicity profile and 82-100% overall response rate, oral propranolol is first-line option in treatment of IH, particularly for complicated and ulcerated forms. It has early, intermediate and long-term pharmacological effect on IH. The early effect is a visible change in colour and softening of the lesion that occurs 1-3 days since the therapy initiation. This is related to the β2 inhibition which results in vasoconstriction due to decreased concentration of vasodilators, such as nitric oxide. The intermediate effect involves inhibition of proangiogenic cascade and angiogenesis as a consequence of VEGF and fibroblast growth factor (FGF) downregulation. The long term effect is due to cell apoptosis resulting in regression of haemangiomas [93]. In the recent consensus, a target daily dose of 1-3 mg/kg has been recommended [94]. Based on a randomized controlled trial performed by Hogeling et al., the treatment should last for at least 6 months which can be modified according to the morphological subtypes [95].

Successful treatment of IH with propranolol leads us to investigate whether this drug is able to present similar anti-tumour activity in RCC that, in fact, is a highly vascularized neoplasm. Its molecular mechanisms of action involve inhibition of signaling pathways that are crucial in RCC development and may be exacerbated by intra-tumour release of stress-related hormones. Propranolol not only inhibits a catecholamine-dependent cancer cell growth and expansion, but simultaneously inhibits VEGF-dependent angiogenesis that is also a main target for currently used drugs in RCC, including sunitinib. Therefore, a combination of propranolol and sunitinib may result in synergistic anti-tumour effect. It is also worthwhile to mention other molecular actions of propranolol that include inhibition of cancer cell proliferation, migration and invasion (Figure 1). Together with reduction of emotional stress related to cancer diagnosis, propranolol may bring multidirectional benefit for RCC patients treated with sunitinib. Additionally, in colon adenocarcinoma, lung adenocarcinoma and melanoma cell lines and mouse models, exogenous NE and chronic stress attenuated the efficacy of sunitinib, primarily through promoting expression of VEGF, IL-6 and IL-8 that was chiefly mediated by β-adrenergic/cAMP/PKA signaling pathway. This negative impact of stress/NE on sunitinib efficacy was blocked by propranolol [96, 97].

All the data mentioned above imply that propranolol may increase efficacy of first-line sunitinib in patients with metastatic RCC. As a safe and well tolerant medication it is widely prescribed in treatment of non-malignant diseases, also within a subgroup of patients with metastatic RCC treated with sunitinib. Furthermore, no significant negative interactions (including life-threatening) between propranolol and sunitinib were reported in the literature. As a hypotensive drug, propranolol would be concomitant and suitable option in management of sunitinib-induced hypertension. Finally, the potential benefit of adding propranolol to a standard-of-care sunitinib would not lead to financial overload as the monthly cost of propranolol is only about $2.

To conclude, the molecular antineoplastic profile of propranolol, its potential synergism with sunitinib, favourable safety profile, hypotensive potential for sunitinib-induced hypertension, ability to reduce cancer-associated anxiety and low cost of intervention encourage us to assess prospectively the combination of propranolol and sunitinib in first-line treatment of metastatic RCC.

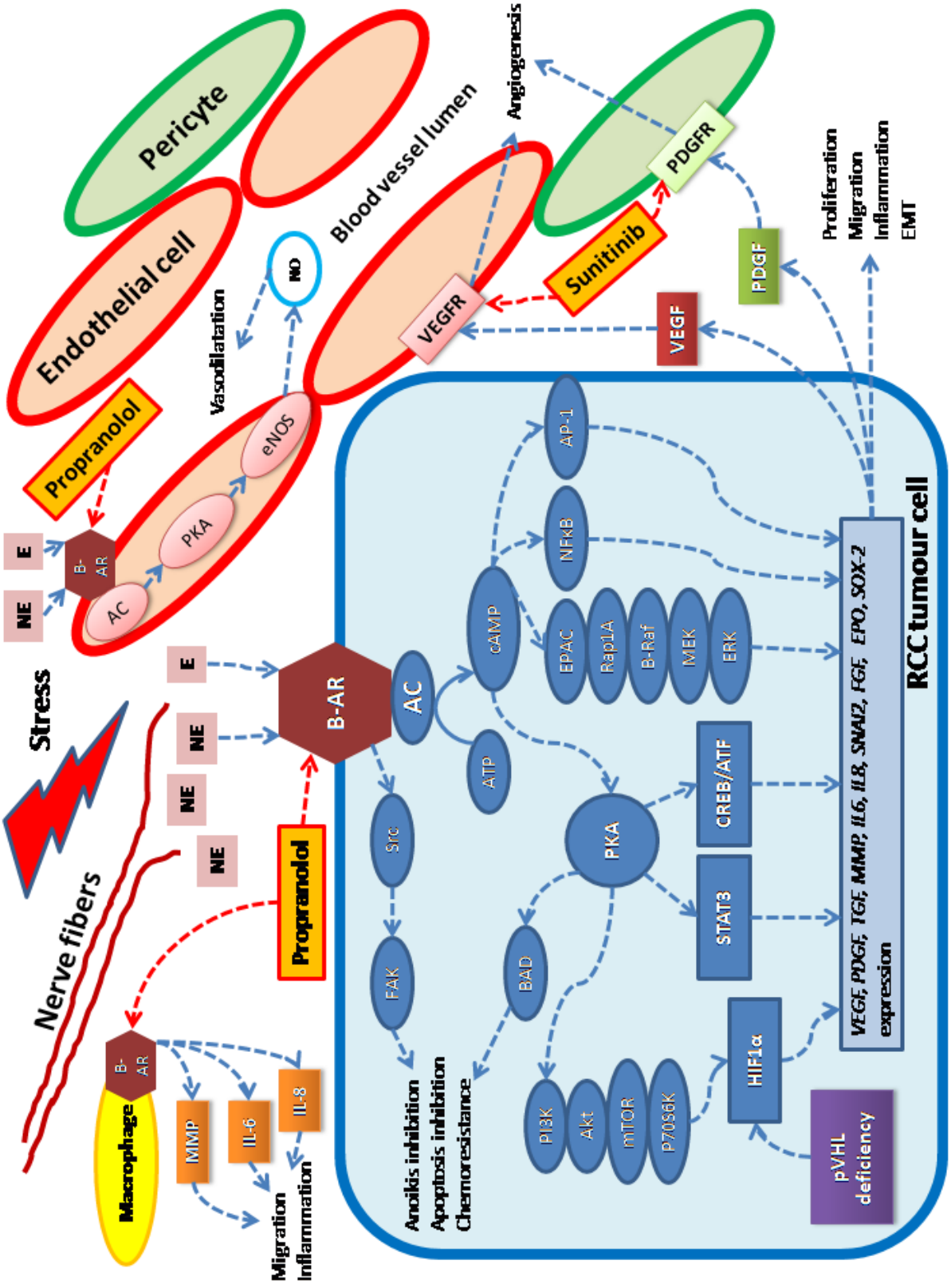

Figure 1. Theoretical model of synergistic anti-tumour activity of propranolol plus sunitinib in RCC.

2. Study Objectives

2.1 Primary Objective

To assess the efficacy of first-line systemic therapy with propranolol plus sunitinib in patients with metastatic RCC.

Primary endpoint:

- objective response rate.

2.2 Secondary Objectives

To assess the efficacy, safety, influence on health-related quality of life and disease-related stress, and relationship between tumour tissue markers and serum biomarkers with treatment and clinical outcomes of first-line systemic therapy with propranolol plus sunitinib in patients with metastatic RCC.

Secondary endpoints:

- overall survival,
- progression-free survival,
- disease control rate,
- incidence of adverse events and serious adverse events,
- changes from baseline in vital signs and laboratory results,
- changes in patient-reported outcomes using The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, version 3) and FACT-Kidney Symptom Index - 15 (FKSI-15),
- changes in patient-reported outcomes using the 10-point Perceived Stress Scale (PSS),
- relationship of the primary tumour tissue and serum biomarkers with treatment and clinical outcomes.

3. Study Design

3.1 Summary of Study Design

The present study is designed as a prospective, interventional, single-arm, single-center, and open-label phase II trial.

The study is planned to have 3 periods (illustrated in Figure 1.):

1. A pre-treatment period – starts at the time of patient's screening, giving him information of the study and writing consent.

2. A treatment period – starts at application of first dose of interventional products under medical supervision and lasts until discontinuation of study treatment.

3. A postdiscontinuation period – starts at the time of discontinuation from study treatment; this period includes a summary (end-of-treatment) visit and will continue until death or the end of study data collection.

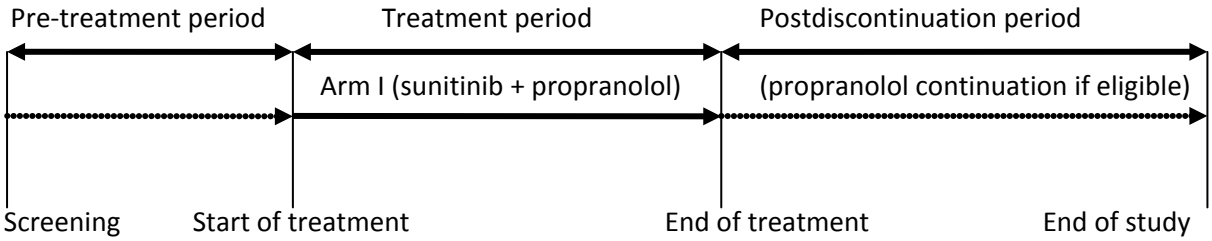

Figure 1. The illustration of study design for Protocol PS-001.

3.2 Length of the Study

Total length of the study is planned to be at least 18 months, including 12 months of accrual time, and then at least 6 months of follow-up time since the last patient recruitment.

3.3 Study Extension

After data final analysis, all remaining on-study patients without disease progression will be permitted to transition into the extension phase of the study to continue to receive treatment until disease progression, death, unacceptable toxicity, patient refusal, or start of any new anticancer treatment, whichever occurs first.

4. Study Population

4.1 Number of Patients Planned

According to the sample size calculation (Section 8.2), maximum number of 33 patients will be enrolled in the study.

4.2 Recruitment of Patients

Candidates for the trial will be recruited from a general population of patients with metastatic RCC, who are planned to start first-line systemic anticancer therapy with sunitinib.

4.3 Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

1. Histological diagnosis of ccRCC or mixed-type RCC with more than 60% of clear-cell component.
2. Diagnosis of stage IV RCC (primary metastatic or recurrence after surgical procedure).
3. Prior nephrectomy (complete or partial).

4. Presence of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

5. Karnofsky performance status (KPS) score of 80-100%.

6. Favourable- or intermediate-risk according to MSKCC criteria.

7. Adequate organ function, including the following:

    a. hepatic: total bilirubin ≤ 2 times the upper limit of normal (excluding patients with Gilbert syndrome), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 times the upper limit of normal,

    b. renal: serum creatinine ≤ 2 times the upper limit of normal,

    c. bone marrow: absolute neutrophil count ≥ 1500/mm^3, platelets ≥ 100000/mm^3, hemoglobin ≥ 9,5 g/dl.

8. Normal thyroid function (natural or with supplementation of thyroid hormones) defined as thyroid-stimulating hormone (TSH) within limits of normal.

9. Age eighteen years or older on the day of consent.

10. Written informed consent prior to study entry.

4.4 Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

1. Prior systemic pharmacotherapy of renal cell carcinoma.

2. Treatment with propranolol within 6 months of study entry.

3. Metastases in central nervous system (patients who had central nervous system metastases that were surgically resected and/or treated with radiotherapy in the past and now are without neurological symptoms, are allowed on protocol).

4. Female patients who are pregnant or breast feeding or adults of reproductive potential who are not using effective birth control methods.

5. Presence of other malignancies (patients with carcinoma in situ of the cervix or basal cell carcinoma of the skin are allowed on protocol).

6. Presence of any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

    a. heart failure of New York Heart Association Class III or IV, significant cardiac arrhythmia or any other clinically significant cardiovascular disease,

    b. unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of entering the study,

c. severely impaired respiration as defined as 0_2 saturation that is ≤ 90% at rest on room air,

d. uncontrolled diabetes as defined by fasting serum glucose > 1,5 times the upper limit of normal,

e. ejection fraction less than 40% (measured at echocardiography),

f. significant liver disease such as cirrhosis, active hepatitis or chronic persistent hepatitis,

g. active (acute or chronic) infections requiring antimicrobial intervention.

7. Concomitant treatment with:

   a. chronic, systemic corticosteroids or another immunosuppressive agent; topical or inhaled corticosteroids are allowed,

   b. strong CYP3A4 inducers/inhibitors: carbamezepine, phenytoin, rifabutin, rifampin, nafcillin, phenobarbital, St John's wort, itraconazole, ketoconazole, erythromycinum, clarithromycinum, nefazodone.

8. Known allergy/sensitivity to sunitinib and/or propranolol.

9. Galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

10. Immunization with attenuated live vaccines within 30 days of study entry.

11. Human immunodeficiency virus (HIV) sero-positivity at the study entry or in the past.

12. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of sunitinib and/or propranolol (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).

13. Presence of active, bleeding diathesis.

14. Major surgery (defined as requiring general anesthesia) and/or significant traumatic injury (requiring > 28 days to heal) within 28 days of the study entry; presence of side effects due to any surgery or probable requirement of major surgery during the course of the study.

15. Present contraindications to propranolol, that include: bronchial asthma, prolonged fasting, acidosis, hypotension (systolic blood pressure less than 90 mmHg, diastolic blood pressure less than 60 mmHg), severe peripheral arterial circulatory disturbance, cardiogenic shock, bradycardia, Prinzmetal's angina, uncontrolled heart failure, second or third degree heart block, untreated phaeochromocytoma, sick sinus syndrome.

16. Inability or unwillingness of subject or legal guardian/representative to give written informed consent.

4.5 Discontinuations

4.5.1 Discontinuation of Patients

Patients will be discontinued from the study in the following circumstances:

1. Withdrawal of informed consent.
2. Evidence of progressive disease (PD) including patient's death.
3. Recurrent or unacceptable toxicity grade ≥ 3 according to The Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
4. Karnofsky performance status < 70 observed in three assessment points (visits) in a row.
5. Development of exclusion criteria or other safety reasons.
6. Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing results.
7. Discontinuation of sunitinib and/or propranolol for more than 14 days (excluding the 2-week rest period for each cycle of sunitinib).
8. Protocol non-compliance.

In all cases, the reason for withdrawal must be recorded in the Case Report Form (CRF) and in the subject's medical records. All patients who discontinue because of adverse events or clinical laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome recorded.

4.5.2 Replacement of Patients

Patients who discontinue due to toxicity related to one or both study drugs will not be replaced. Patients who discontinue during the first two weeks due to reasons other than toxicity will be replaced.

4.5.3 Discontinuation of the Study

The study will be discontinued if the Investigators judge it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

5. Study Interventions

5.1 Investigational Products

5.1.1 Sunitinib (SUTENT® by Pfizer Inc.)

Marketing Authorisation Holder:
Pfizer Limited
Ramsgate Road

Sandwich, Kent CT13 9NJ
United Kingdom

Presentation of sunitinib 50 mg: gelatin capsules with caramel cap and caramel body, printed with white ink “Pfizer” on the cap, “STN 50 mg” on the body and containing yellow to orange granules.

Presentation of sunitinib 37.5 mg: gelatin capsules with yellow cap and yellow body, printed with black ink “Pfizer” on the cap, “STN 37.5 mg” on the body and containing yellow to orange granules.

Presentation of sunitinib 25 mg: gelatin capsules with caramel cap and orange body, printed with white ink “Pfizer” on the cap, “STN 25 mg” on the body and containing yellow to orange granules.

Presentation of sunitinib 12.5 mg: Gelatin capsules with orange cap and orange body, printed with white ink “Pfizer” on the cap, “STN 12.5 mg” on the body, and containing yellow to orange granules.

Modalities of administration: 1 capsule (50 mg or 37.5 mg [alternatively: 1 capsule 25 mg + 1 capsule 12.5 mg] or 25 mg) every day during the treatment period. Capsule must be administered orally, with or without food.

Dosage: starting dose is 50 mg taken once daily, for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks. The schedule may be changed by the Investigator to 2 weeks on / 1 week off to decrease the level of toxic effects. Dose modifications in 12.5 mg steps may be applied based on individual safety and tolerability. Daily dose cannot be either decreased below 25 mg or increased over 50 mg. If there are suspicions of its unacceptable toxicity, it must be withdrawn immediately.

There is no specific antidote for overdose with sunitinib and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed active substance may be achieved by emesis or gastric lavage.

5.1.2 Propranolol (Propranolol Accord® by Accord Healthcare Ltd.)

Marketing Authorisation Holder:
Accord Healthcare Limited
319, Pinner Road,
North Harrow,
Middlesex HA1 4HF,
United Kingdom

Presentation of propranolol 40 mg: white to off-white round, biconvex film-coated tablets imprinted with 'AL' on one side and a score line on the other side. Diameter of the tablet is 9.0 mm. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
Modalities of administration: prespecified number of propranolol tablets every day during treatment period. In case of administration two times a day, tablet(s) must be administered orally in the morning and in the evening. In case of administration three times a day, tablet(s) must be administered orally in the morning, in the afternoon and in the evening.

Dosage: it is obligatory to follow the schedule presented below:

1. the starting dose is 40 mg (one tablet) two times a day (total daily dose of 80 mg); if the drug is well tolerated the dose should be increased to a dose mentioned in point 2., but not faster than 7 days of the current dose; if the drug is badly tolerated, the drug should be withdrawn and the patient should discontinue propranolol treatment;

2. the next dose is 80 mg (two tablets) two times a day (total daily dose of 160 mg); if the drug is well tolerated the dose should be increased to a dose mentioned in point 3., but not faster than 7 days of the current dose; if the drug is badly tolerated, the dose should be decreased to that mentioned in point 1. or withdrawn in case of severe toxicity;

3. the next dose is 80 mg (two tablets) three times a day (total daily dose of 240 mg); if the drug is well tolerated the dose may not be increased; if the drug is badly tolerated, the dose should be decreased to that mentioned in point 2. or point 1. or withdrawn in case of severe toxicity.

In case of propranolol overdose, atropine 1 to 2 mg intravenously can counter excessive bradycardia. If necessary this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be followed or repeated by an intravenous infusion of glucagon 1 to 10 mg/hour depending on response. If no response is received to the glucagon or if glucagon is unavailable, a beta-adrenoceptor stimulant e.g. dobutamine 2.5 to 10 microgram/kg/minute by intravenous infusion may be given. Bronchospasm may be treated by nebulized salbutamol or intravenous aminophylline or salbutamol. Severe cases may require the use of oxygen or artificial ventilation.

When it has been decided to interrupt a β-blockade in preparation for surgery, therapy should be discontinued for at least 48 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation; however the risk of hypotension may be increased as well. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. The patient may be protected against vagal reactions by intravenous administration of atropine.

5.2 Concomitant Treatment

5.2.1 Prohibited Concomitant Treatment

- Any drugs that have been approved in antitumor therapies or any new potentially antineoplastic agents that are being investigated (e.g. IL-2, IFN, cabozantinib, sorafenib, axitinib, dovitinib, pazopanib, lenvatinib, everolimus, temsirolimus, nivolumab, ipilimumab).

- CYP3A4 inducers/inhibitors: carbamezepine, phenytoin, rifabutin, rifampin, nafcillin, phenobarbital, St John's wort, itraconazole, ketoconazole, erythromycinum, clarithromycinum, nefazodone.

- Immunosuppressors and immunomodulators including chronic systemic corticosteroids.

- β-agonists, β-blockers other than propranolol, bronchodilators, calcium channel blockers (verapamil, diltiazem or bepridil), fingolimod, barbiturates, propafenone, monoamine oxidase inhibitors.

- attenuated live vaccines.

5.2.2 Permitted Concomitant Treatment

Any drugs other than those listed above are allowed, and should be administered, as necessary for the treatment of the patient, when possible with a stable dose, at the discretion of the Investigator. All treatment with these drugs should be recorded on the appropriate CRF.

5.3 Storage, Accountability and Compliance

All study drugs must be kept in a secure place under adequate storage conditions – protected from moisture and light. The patient will record the use of study medications in the Patient's Diary on a daily basis and the adherence to the prescribed treatment will be checked at every clinic visit. If there are at least 14 days without study drugs intake (excluding a 14 days off the sunitinib in each cycle), patient should be discontinued from the study.

6. Study Measures

6.1 Definitions of Efficacy Measures

6.1.1 Objective Response Rate

Objective Response Rate (ORR) is defined as the percentage of patients who have achieved partial response (PR) and complete response (CR) according to RECIST guidelines (version 1.1).

6.1.2 Progression-free Survival

Progression-Free Survival (PFS) is defined as the time from the date of first dose investigational products administration to the first date of objectively determined progressive disease (PD) according to RECIST guidelines (version 1.1) or death from any cause. For patients not known to have died as of the data cut-off date and who do not have objective PD, PFS will be censored at the date of the last RECIST (version 1.1) assessment.

6.1.3 Overall Survival

Overall Survival (OS) is defined as the time from the date of first dose investigational products administration to the date of death from any cause. For patients not known to have died as of the data cut-off date, OS will be censored at the last contact date.

6.1.4 Disease Control Rate

Disease Control Rate (DCR) is defined as the percentage of patients who have achieved partial response (PR), complete response (CR) and stable disease (SD) according to RECIST guidelines (version 1.1).

6.2 Safety Measures

Safety evaluation will rely on capturing all adverse events reported on vital signs, physical examinations and laboratory tests. The CTCAE (version 4.0) will be used to standardize reported adverse events of any kind.

6.3 Health-related Quality of Life Measures

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 version 3) and FACT-Kidney Symptom Index - 15 (FKSI-15) are validated and reliable self-administered instruments that will be used to assess health-related quality of life.

6.4 Disease-related Stress Measures

The 10-point Perceived Stress Scale (PSS) is validated and reliable self-administered instrument that will be used to assess Disease-related Stress (DRS).

6.5 Tumour Tissue and Serum Biomarkers Assessments

Formalin-fixed paraffin embedded primary tumour tissue (archival or recently biopsied) and serum biomarkers will be used for exploratory analysis of potential pathway components or modulators associated with RCC or the mechanism(s) of action of the study drugs.

6.6 Timing and Methods of Measurements

6.6.1 Pre-treatment Period

The protocol presents scheduled timelines for study procedures by abbreviated references to week (W) and day (D) (eg, W1D1, W3D1 etc) relative to the date of the first dose of study treatment (defined as W1D1).

Patients will be examined within 7 days prior to the first ingestion of the investigational products during a screening visit to assess their eligibility to participate. Each subject will consent in writing to the screening process before the start of the examination. The consent form will also include the study information leaflet. The examinations and investigations will include:

- medical history, including history of concomitant chronic diseases, allergies, use of medications, demographics (date of birth, sex, race), alcohol and tobacco consumption patterns, family history of cancer,
- physical examination including assessment of general appearance, mouth, throat, cardiovascular, lungs, abdomen and measurement of height and body weight. The examination will be made in accordance with the normal clinical routines at the trial center,
- vital signs: systolic and diastolic blood pressure, heart rate, pulse, respiratory rate, 0_2 saturation and body temperature,
- KPS score,
- electrocardiography (ECG): standard 12-lead,
- 24-hour Holter ECG monitoring,
- echocardiography,
- cardiology consultation,

- laboratory tests:
    - ❖ hematology: a complete blood count with hemoglobin level,
    - ❖ serum biochemistry including levels of: creatinine, urea, bilirubin, AST, ALT, LDH, TSH, alkaline phosphatase (ALP) albumin, sodium, potassium, calcium (total),
    - ❖ coagulation: Activated Partial Thromboplastin Time (APTT), International Normalized Ratio (INR)
    - ❖ routine urine analysis,
    - ❖ serum β-HCG pregnancy test in fertile females,
    - ❖ HIV testing by the enzyme-linked immunosorbent assay (ELISA) +/- Western blot.
- filling in EORTC QLQ-C30 and FKSI questionnaires,
- filling in the PSS questionnaire,
- collection of blood samples for serum biomarkers,
- collection of formalin-fixed paraffin embedded primary tumour tissue whenever available.

Corrected calcium level will be calculated using formula:

Corrected calcium level [mg/dl] = total calcium level [mg/dl] + 0.8 x (4.0 - albumin level [g/dL])

Within 4 weeks before the start of therapy, baseline tumor measurement(s) will be performed on each patient. Computed tomography (CT) and magnetic resonance imaging (MRI) are allowed methods of measurement. The study will not permit ultrasound, chest-X-ray or positron emission tomography (PET) scans as methods of tumor measurement.

6.6.2 Treatment Period

During every day of the treatment period, patient will have to collect blood pressure and pulse measures two times a day (in the morning and in the evening) and to record the results in the Patient's Diary.

The examinations and investigations during control visits, that will take place every 6 weeks of treatment, will include:

- physical examination,
- vital signs measurement,
- laboratory tests:
    - ❖ hematology: a complete blood count with hemoglobin level,

- ❖ serum biochemistry including levels of: creatinine, urea, bilirubin, AST, ALT, ALP, LDH, albumin, sodium, potassium, calcium (total),

- standard 12- lead ECG,
- filling in the EORTC QLQ-C30 and FKSI-15 questionnaires,
- filling in the PSS questionnaire.

At the start of the second and third week of the treatment (W2D1 and W3D1), additional visit is planned to assess safety of propranolol and to define further propranolol dose and will include physical examination, vital signs measurement, verification of ambulatory blood pressure and pulse measures, ECG (12-lead) and optional cardiology consultation.

Blood samples for serum biomarkers will be obtained at W7D1.

The method used at baseline to assess tumor measurement(s) must be used consistently and will be repeated every 12 weeks (± 2 weeks). Tumor responses will be measured and recorded using the RECIST guidelines (version 1.1).

6.6.3 Postdiscontinuation Period

Patients will continue treatment until they require discontinuation of study drugs for any reason mentioned in Section 4.5.1 of this document (including disease progression). Each enrolled patient will enter a postdiscontinuation period once study treatment is discontinued. The end-of-treatment visit will take place within 30 days after discontinuation of the study drugs and will include:

- physical examination,
- vital signs measurement,
- laboratory tests:
  - ❖ hematology: a complete blood count with hemoglobin level,
  - ❖ serum biochemistry including levels of: creatinine, urea, bilirubin, AST, ALT, ALP, LDH, TSH, albumin, sodium, potassium, calcium (total),
  - ❖ coagulation: APTT, INR,
- standard 12- lead ECG,
- 24-hour Holter ECG monitoring,
- echocardiography,
- cardiology consultation,
- filling in the EORTC QLQ-C30 and FKSI-15 questionnaires,

- filling in the PSS questionnaire,
- blood samples for serum biomarkers.

During the postdiscontinuation period, information about date of disease progression, death, adverse events, subsequent anticancer systemic therapy, radiotherapy, or surgical intervention will be collected.

In case of disease progression and the need for second-line anticancer therapy, propranolol may be continued beyond first-line progression if the drug is well tolerated and there are other indications to continue β-adrenergic blockade. It may be also replaced by other β-blocker, if necessary. Cessation of propranolol therapy should be gradual.

6.6.4 Unscheduled Visits or Assessments

If the investigator determines that a subject should be monitored more frequently or with additional laboratory parameters assessments than indicated by the protocol-defined visit schedule, unscheduled visits or assessments are permitted. Unscheduled visits for radiographic evaluations are allowed at any time as clinically indicated.

7. Adverse Events

7.1 Adverse Events Definitions

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition during treatment. However, it does not necessarily have to have a causal relationship with this treatment.

A Serious Adverse Event (SAE) is an adverse event occurring during any phase of the study and at any dose of the investigational product which fulfils one or more of the following criteria:

- results in death,
- is life-threatening (it refers to an event in which the patient was at risk of death at the time of the event),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity.

7.2 Expected Adverse Events

7.2.1 Expected Adverse Events for Sunitinib

Adverse reactions related to sunitinib are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); Frequency not known (cannot be estimated from the available data).
The following undesired events, listed by body system, have been reported:

Blood and lymphatic system disorders

Very common: neutropoenia, thrombocytopenia, anaemia, leucopoenia.

Common: lymphopoenia.

Uncommon: pancytopenia.

Rare: thrombotic microangiopathy.

Immune system disorders

Uncommon: hypersensitivity.

Rare: angioedema.

Endocrine disorders

Very common: hypothyroidism.

Uncommon: hyperthyroidism.

Rare: thyroiditis.

Infections and infestations

Common: viral infections, respiratory infections, abscess, fungal infections, urinary tract infection, skin infections, sepsis.

Uncommon: necrotising fasciitis, bacterial infections.

Metabolism and nutrition disorders

Very common: decreased appetite.

Common: dehydration, hypoglycaemia.

Rare: tumour lysis syndrome.

Psychiatric disorders

Very common: insomnia.

Common: depression.

Nervous system disorders

Very common: dizziness, headache, taste disturbance.

Common: neuropathy peripheral, paraesthesia, hypoaesthesia, hyperaesthesia.

Uncommon: cerebral haemorrhage, cerebrovascular accident, transient ischaemic attack.

Rare: posterior reversible encephalopathy syndrome.

Eye disorders

Common: periorbital oedema, myelid oedema, lacrimation increased.

Cardiac disorders

Common: myocardial ischemia, ejection fraction decreased.

Uncommon: cardiac failure congestive, myocardial infarction, cardiac failure, cardiomyopathy, pericardial effusion, ECG QT prolonged.

Rare: left ventricular failure, torsade de pointes.

Vascular disorders

Very common: hypertension.

Common: deep vein thrombosis, hot flush, flushing.

Uncommon: tumour haemorrhage.

Respiratory, thoracic and mediastinal disorders

Very common: dyspnoea, epistaxis, cough.

Common: pulmonary embolism, pleural effusion, haemoptysis, dyspnoea exertional, oropharyngeal pain, nasal congestion, nasal dryness.

Uncommon: pulmonary haemorrhage, respiratory failure.

Gastrointestinal disorders

Very common: stomatitis, abdominal pain, vomiting, diarrhea, dyspepsia, nausea, constipation.

Common: gastro-oesophageal reflux disease, dysphagia, gastrointestinal haemorrhage, oesophagitis, abdominal distension, abdominal discomfort, rectal haemorrhage, gingival bleeding, mouth ulceration, proctalgia, cheilitis, haemorrhoids, glossodynia, oral pain, dry mouth, flatulence, oral discomfort, eructation.

Uncommon: gastrointestinal perforation, pancreatitis, anal fistula.

Hepatobiliary disorders

Uncommon: hepatic failure, cholecystitis, hepatic function abnormal.

Rare: hepatitis.

Skin and subcutaneous tissue disorders

Very common: skin discolourations, palmar-plantar erythrodysaesthesia syndrome, rash, hair colour changes, dry skin.

Common: skin exfoliation, skin reaction, eczema, blister, erythema, alopecia, acne, pruritus, skin hyperpigmentation, skin lesion, hyperkeratosis, dermatitis, nail disorder.

Rare: erythema multiforme, Stevens-Johnson syndrome, pyoderma gangrenosum, toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders

Very common: pain in extremity, arthralgia, back pain.

Common: musculoskeletal pain, muscle spasms, myalgia, muscular weakness.

Uncommon: osteonecrosis of the jaw, fistula.

Rare: rhabdomyolysis, myopathy.

Renal and urinary disorders

Common: renal failure, renal failure acute, chromaturia, proteinuria.

Uncommon: haemorrhage urinary tract.

Rare: nephrotic syndrome.

General disorders and administration site conditions

Very common: mucosal inflammation, fatigue, oedema, pyrexia.

Common: chest pain, pain, influenza like illness, chills.

Uncommon: impaired healing.

Investigations

Common: Weight decreased, white blood cell count decreased, lipase increased, platelet count decreased, haemoglobin decreased, amylase increased, aspartate aminotransferase increased, alanine aminotransferase increased, blood creatinine increased, blood pressure increased, blood uric acid increased.

Uncommon: blood creatine phosphokinase increased, blood thyroid stimulating hormone increased.

7.2.2 Expected Adverse Events for Propranolol

Adverse reactions related to propranolol are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); Frequency not known (cannot be estimated from the available data).

The following undesired events, listed by body system, have been reported:

Blood and lymphatic system disorders

Rare: thrombocytopenia.
Frequency not known: agranulocytosis.
Immune system disorders
Rare: angioedema.
Endocrine disorders
Frequency not known: masking signs of thyrotoxicosis.
Metabolic and nutritional disorders
Frequency not known: hypoglycaemia in neonates, infants, children, elderly patients, patients on haemodialysis, patients on concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported. Changes in lipid metabolism (changes in blood concentrations of triglycerides and cholesterol). Severe hypoglycemia may rarely lead to seizures or coma.
Psychiatric disorders
Common: sleep disturbances, nightmares.
Rare: Hallucinations, psychoses, mood changes
Frequency not known: depression.
Nervous system disorders
Rare: confusion, memory loss, dizziness, paraesthesia.
Very rare: Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported.
Frequency not known: headache, seizure linked to hypoglycaemia.
Eye disorders
Rare: visual disturbances, dry eyes.
Frequency not known: conjunctivitis.
Cardiac disorders
Common: bradycardia.
Rare: Heart failure deterioration, precipitation of heart block, postural hypotension which may be associated with syncope.
Frequency not known: worsening of attacks of angina pectoris.
Vascular disorders
Common: cold extremities, Raynaud's syndrome.
Rare: exacerbaction of intermittent claudication.
Respiratory thoracic and mediastinal disorders
Common: breathlessness.
Rare: Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome.
Frequency not known: dyspnoea.
Gastrointestinal disorders
Uncommon: diarrhoea, nausea, vomiting.
Frequency not known: constipation, dry mouth.
Skin and subcutaneous tissue disorders
Rare: alopecia, purpura, psoriasiform skin reactions, exacerbation of psoriasis, rash.
Very rare: isolated cases of hyperhidrosis have been reported.
Musculoskeletal system and connective tissue disorders

Frequency not known: arthralgia.

Renal and urinary disorders

Frequency not known: reduced renal blood flow and GFR.

Reproductive system and breast disorders

Frequency not known: impotence.

General disorders and administration site conditions

Common: fatigue and/or lassitude (often transient).

Investigations:

Very rare: An increase in antinuclear antibodies (ANA) has been observed with many β-blockers, however the clinical relevance of this is not clear.

7.3 Adverse Events Management

If any adverse event occurs, all appropriate measurements to ensure the safety of the patients must be taken. The investigator has to care about patient with best medical knowledge and available methods of treatment and should follow up the outcome of adverse events (clinical signs, laboratory values or other, etc) until the return to normal or stabilization of the patient's condition. Dose modification for drug induced toxicity should be kept with accordance to Summary of Product Characteristics of all used drugs.

7.4 Adverse Events Monitoring and Reporting

All Adverse Events regardless of seriousness or relationship to investigational products have to be recorded on the corresponding page(s) included in the CRF. The Investigator should specify the date of onset, intensity, action taken with respect to investigational products, corrective treatment/therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the investigational products.

In the case of a SAE the Investigator must send the signed and dated corresponding page(s) in the CRF to the representative of the Monitoring Team and attach a copy of all examinations carried out with dates on which these examinations were performed.

8. Statistical Considerations

8.1 Study Hypotheses

Primary hypothesis is whether addition of oral propranolol to sunitinib in first-line treatment of metastatic RCC can increase its antitumor efficacy and it is related to analyses of: ORR, PFS, OS, and DCR.

Secondary hypothesis is whether addition of oral propranolol to sunitinib in first-line treatment of metastatic RCC is safe and has an influence on patient-reported quality of life and disease-related stress and it is referred to analyses of: adverse events, vital signs, physical examinations, laboratory tests, health-related quality of life and disease-related stress.

8.2 Sample Size Calculation

According to registration study for sunitinib and a recent population-based study, the ORR of sunitinib monotherapy is estimated to be around 30% [46, 47]. Because strong potential bias exists due to single-center and phase II study design, we assume an increase to 55% of the ORR under propranolol plus sunitinib therapy as a combination worthwhile for further investigation.

The optimal two-stage Simon design is to test the null hypothesis that $P \leq 0.300$ versus the alternative that $P \geq 0.550$ has an expected sample size of 17.36 and a probability of early termination of 0.869. If the combination of propranolol and sunitinib is actually not effective, there is a 0.050 probability of concluding that it is (the target for this value [α level] was 0.050). If the combination is actually effective, there is a 0.195 probability of concluding that it is not (the target for this value [β-level] was 0.200). After testing the combination on 15 patients in the first stage, the trial will be terminated if 6 or fewer achieve ORR. If the trial goes on to the second stage, a total of 33 patients will be studied. If the total number achieving ORR is less than or equal to 13, the combination is rejected.

8.3 General Considerations

The analyses will be performed on all patients who received at least one dose of study medications.

Descriptive statistics, including the mean, standard deviation, median, interquartile range, minimum, and maximum values will be provided for continuous variables as well as frequencies and percentages for categorical variables.

Characteristics such as patient age, gender, height, weight, medical history, and Karnofsky performance status, concomitant therapies, as well as baseline signs and symptoms will be tabulated.

Study drug administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered, dose intensity, and reasons for the deviations from planned therapy.

A detailed description of patient disposition will be provided. It will include: summary of patients screened, total number of patients enrolled, total number of patients discontinuing the study. A detailed summary of reasons for patient discontinuation from study treatment will be provided.

8.4 Primary and Secondary Endpoints Analyses

8.4.1 ORR and DCR Analysis

The response (CR, PR, SD, PD, ORR, and DCR according to RECIST guidelines (version 1.1)) will be summarized for studied patients as frequency and percentages with 2-sided 95% CI calculated using the Clopper-Pearson method.

To indirectly compare ORR and DCR of patients treated with propranolol and sunitinib combination versus sunitinib monotherapy, a group of patients treated with sunitinib monotherapy will be drawn from the institution historical cohort. This control group will consist of 33 consecutive patients that started sunitinib monotherapy just before the beginning of the present study. The comparison will be

made using unstratified Pearson χ2 test or the Fisher's exact test (in case of no more than 5 expected frequencies in each cell of a studied contingency table) and the Cochran-Mantel-Haenszel test stratified by the MSKCC risk group (favourable versus intermediate). This additional analysis is planned only if the trial goes on to the second stage.

8.4.2 PFS and OS Analysis

PFS and OS will be summarized using Kaplan-Meier method and displayed graphically as cumulative probability of survival (Y axis) versus time since treatment initiation (X axis). The median event time and corresponding 2-sided 95% CI for the median will be provided using log-log transformation.

In an exploratory analysis that aims to identify independent prognostic factors for OS and PFS, the multivariable Cox proportional hazards regression will be used. The variables with p value less than 0.05 will be assumed as independently affecting OS and PFS.

To indirectly compare OS and PFS of patients treated with propranolol and sunitinib combination versus sunitinib monotherapy, a group of patients treated with sunitinib monotherapy will be drawn from the institution historical cohort. This control group will consist of 33 consecutive patients that started sunitinib monotherapy just before the beginning of the present study. The comparison will be made using the unadjusted log-rank test and the adjusted log-rank test based on the inverse probability of treatment weighting [97]. The unstratified and stratified by the MSKCC risk group (favourable versus intermediate) multivariable Cox proportional hazards regression will be used to assess the impact of the drug combination on OS and PFS.

8.4.3 Safety Analysis

Summary tables will present the number of patients observed with adverse events and corresponding percentages. Additionally, the following safety-related outcomes will be summarized: study treatment discontinuations due to adverse events, deaths during the study treatment period, severe adverse events during the study treatment period, hospitalizations and transfusions during the study treatment period.

Each vital sign will be summarized and presented by treatment group. Patients with significant changes in vital signs will be listed.

8.4.4 Health-related Quality of Life Analysis

Descriptive statistics including the mean, standard deviation and 95% CI will be used to summarize absolute scores for EORTC QLQ-C30 and FKSI-15 questionnaires.

A non-parametric Friedman's Analysis of Variance (ANOVA) will be performed to assess the differences in HRQoL outcomes at all studied time-points. In case of significant result Friedman's ANOVA, the difference between two prespecified time-points will be assessed using Nemenyi post-hoc test.

8.4.5 Disease-related Stress Analysis

Descriptive statistics including the mean, standard deviation and 95% CI will be used to summarize absolute scores for 10-point PSS questionnaire.

A non-parametric Friedman's ANOVA will be performed to assess the differences in DRS outcomes at all studied time-points. In case of significant result Friedman's ANOVA, the difference between two prespecified time-points will be assessed using Nemenyi post-hoc test.

8.4.6 Biomarker Analyses

The influence of primary tumour and serum biomarkers on efficacy and safety parameters will be additionally explored if the collection of biological material will be sufficient.

8.5 Interim Analysis

No interim analysis is planned.

8.6 Statistical Software

The sample size calculation was performed using PASS 14 Power Analysis and Sample Size Software, NCSS, LLC, USA.

The remaining calculations will be performed using Stata Software, version 14.2, StataCorp, USA, and R, version 3.2.3, The R Foundation for Statistical Computing, Austria.

9. Ethical and Regulatory Standards

9.1 Ethics Review

The final study protocol, including the final version of the Subject Information and Consent Form (SICF), must be approved in writing by an IRB. All Investigators are responsible for informing the IRB of any SAEs and amendment to the protocol as per regulatory requirement.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirements.

9.3 Subject Information and Consent

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The patients must also be notified that they are free to discontinue from the study at any time. The patients should be given the opportunity to ask questions and allowed time to consider the information provided. The Investigator must store the original, signed patient informed SICF and a copy must be given to the patient.

9.4 Laws and Regulations

This clinical trial will be conducted in compliance with all international and national laws and regulations of the country in which the clinical trial is performed, as well as any applicable guidelines. The trial will be registered on www.clintrials.gov and on other sites, as appropriate.

9.5 Conditions for Modifying the Protocol

Protocol modifications will be prepared, reviewed, and approved by the Investigators. All protocol modifications must be submitted to the IRB for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change involves only logistical or administrative aspects of the trial.

9.6 Insurance

All patients participating in the study will have insurance coverage by the National Health Fund.

10. Bibliographic References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 10 May 2017.
2. Cancer Facts and Figures 2016. American Cancer Society, 2016. Available from: https://old.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf, accessed on 2 Apr 2017.
3. Surveillance Epidemiology and End Results. SEER Stat Fact Sheets. National Cancer Institute. Available from: http://seer.cancer.gov/statfacts/html/kidrp.html, accessed on 10 May 2017.
4. Lopez-Beltran A, Carrasco JC, Cheng L, et al. 2009 update on the classification of renal epithelial tumors in adults. Int J Urol. 2009; 16:432-43.
5. Collins ET. Intra-ocular growths (two cases, brother and sister, with peculiar vascular new growth, prob- ably retinal, affecting both eyes). Trans Ophthalmol Soc UK. 1894; 14:141-9.
6. von Hippel E. Ueber eine sehr seltene Erkrankung der Nethaut. Graefe Arch Ophthalmol. 1904; 59:83-106.
7. Lindau A. Zur Frage der Angiomatosis Retinae und Ihrer Hirncomplikation. Acta Opthalmol. 1927; 4:193-226.
8. Latif F, Tory K, Gnarra J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. Science. 1993; 260:1317-20.
9. Maher ER, Neumann HP, Richard S. von Hippel-Lindau disease: a clinical and scientific review. Eur J Hum Genet. 2011; 19:617-23.
10. Lee S, Neumann M, Stearman R, et al. Transcription-dependent nuclear-cytoplasmic trafficking is required for the function of the von Hippel-Lindau tumor suppressor protein. Mol Cell Biol. 1999; 19:1486-97.
11. Oya M, Takayanagi A, Horiguchi A, et al. Increased nuclear factor-kappa B activation is related to the tumor development of renal cell carcinoma. Carcinogenesis. 2003; 24:377-84.
12. Gao C, Cao W, Bao L, et al. Autophagy negatively regulates Wnt signalling by promoting Dishevelled degradation. Nat Cell Biol. 2010; 12:781-90.
13. Pfaffenroth EC, Linehan M. Genetic basis for kidney cancer: Opportunity for disease-specific approaches to therapy. Expert Opin Biol Ther. 2008; 8:779-90.
14. Bader HL, Hsu T. Systemic VHL gene functions and the VHL disease. FEBS Lett. 2012; 586:1562-9.

15. Nickerson ML, Jaeger E, Shi Y, et al. Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. Clin Cancer Res. 2008; 14 (15):4726-34.
16. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012; 366(10):883-92.
17. Daly CJ, McGrath JC. Previously unsuspected widespread cellular and tissue distribution of betaadrenoceptors and its relevance to drug action. Trends Pharmacol Sci. 2011; 32:219-26.
18. Montminy M. Transcriptional regulation by cyclic AMP. Annu Rev Biochem. 1997; 66:807-22.
19. Zhang X, Odom DT, Koo SH, Conkright MD, Canettieri G, Best J, et al. Genome-wide analysis of cAMP-response element binding protein occupancy, phosphorylation, and target gene activation in human tissues. Proc Natl Acad Sci U S A. 2005; 102:4459-64.
20. de Rooij J, Zwartkruis FJ, Verheijen MH, et al. Epac is a Rap1 guanine-nucleotide-exchange factor directly activated by cyclic AMP. Nature. 1998; 396:474-7.
21. Schuller HM, Al-Wadei HA. Neurotransmitter receptors as central regulators of pancreatic cancer. Future Oncol 2010; 6:221-8.
22. Thaker PH, Han LY, Kamat AA, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nat Med 2006; 12:939-44.
23. Al-Wadei HA, Ullah MF, Al-Wadei MH. Intercepting neoplastic progression in lung malignancies via the beta adrenergic (beta-AR) pathway: implications for anti-cancer drug targets. Pharmacol Res 2012; 66:33-40.
24. Lang K, Lt Drell T, Lindecke A, et al. Induction of a metastatogenic tumor cell type by neurotransmitters and its pharmacological inhibition by established drugs. Int J Cancer 2004; 112:231-8.
25. Park SY, Kang JH, Jeong KJ, et al. Norepinephrine induces VEGF expression and angiogenesis by a hypoxia-inducible factor-1alpha protein-dependent mechanism. Int J Cancer 2011; 128:2306-16.
26. Sood AK, Armaiz-Pena GN, et al. Adrenergic modulation of focal adhesion kinase protects human ovarian cancer cells from anoikis. J Clin Invest. 2010; 120: 1515-23.
27. Sastry KS, Karpova Y, Prokopovich S, et al. Epinephrine protects cancer cells from apoptosis via activation of cAMP-dependent protein kinase and BAD phosphorylation. J Biol Chem. 2007; 282:14094-100.
28. Armaiz-Pena GN, Allen JK, Cruz A, et al. Src activation by beta-adrenoreceptors is a key switch for tumour metastasis. Nat Commun 2013; 4:1403.
29. Shahzad MM, Arevalo JM, Armaiz-Pena GN, et al. Stress effects on FosB- and interleukin-8 (IL8)-driven ovarian cancer growth and metastasis. J Biol Chem 2010; 285:35462-70.
30. Sloan EK, Priceman SJ, Cox BF, et al. The sympathetic nervous system induces a metastatic switch in primary breast cancer. Cancer Res 2010; 70:7042-52.
31. Hara MR, Kovacs JJ, Whalen EJ, Rajagopal S, Strachan RT, Grant W, et al. A stress response pathway regulates DNA damage through beta2-adrenoreceptors and beta-arrestin-1. Nature. 2011; 477:349-53.
32. Inbar S, Neeman E, Avraham R, Benish M, Rosenne E, Ben-Eliyahu S. Do stress responses promote leukemia progression? An animal study suggesting a role for epinephrine and prostaglandin-E2 through reduced NK activity. PLoS One. 2011; 6:e19246.
33. Collado-Hidalgo A, Sung C, Cole S. Adrenergic inhibition of innate anti-viral response: PKA blockade of Type I interferon gene transcription mediates catecholamine support for HIV-1 replication. Brain Behav Immun. 2006; 20:552-63. Epub 2006 Feb 2028.

34. Gu L, Lau SK, Loera S, Somlo G, Kane SE. Protein kinase A activation confers resistance to trastuzumab in human breast cancer cell lines. Clin Cancer Res. 2009; 15:7196-206.
35. Cole SW, Sood AK. Molecular pathways: beta-adrenergic signaling in cancer. Clin Cancer Res. 2012; 18:1201-6.
36. Lutgendorf SK, Degeest K, Dahmoush L, et al. Social isolation is associated with elevated tumor norepinephrine in ovarian carcinoma patients. Brain Behav Immun. 2011; 25:250-5.
37. Lutgendorf SK, Degeest K, Sung CY, Arevalo JM, Penedo F, Lucci J 3rd, et al. Depression, social support, and beta-adrenergic transcription control in human ovarian cancer. Brain Behav mmun. 2009; 23:176-83.
38. Cole S, Arevalo J, Takahashi R, Sloan EK, Lutgendorf S, Sood AK, et al. Computational identification of gene-social environment interaction at the human IL6 locus. Proc Natl Acad Sci U S A. 2010; 107:5681-6.
39. Sloan EK, Capitanio JP, Tarara RP, Mendoza SP, Mason WA, Cole SW. Social stress enhances sympathetic innervation of primate lymph nodes: mechanisms and implications for viral pathogenesis. J Neurosci. 2007; 27:8857-65.
40. Mickisch GH, Garin A, van Poppel H, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomized trial. Lancet 2001; 358:966.
41. Heng DY, Wells JC, Rini BI, et l. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur Urol. 2014; 66:704-10.
42. Ljungberg B. The role of metastasectomy in renal cell carcinoma in the era of targeted therapy. Curr Urol Rep 2013; 14:19-25.
43. Van der Poel HG, Roukema JA, Horenblas S, et al. Metastasectomy in renal cell carcinoma: A multicenter retrospective analysis. Eur Urol 1999; 35(3):197-203.
44. Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Français d'Immunothérapie. N Engl J Med 1998; 338(18):1272-8.
45. Greef B, Eisen T. Medical treatment of renal cancer: new horizons. Br J Cancer. 2016; 115:505-16.
46. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007; 356(2):115-24.
47. Ruiz-Morales JM, Swierkowski M, Wells JC, et al. First-line sunitinib versus pazopanib in metastatic renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur J Cancer. 2016; 65:102-8.
48. Bracarda S, Iacovelli R, Boni L et al. Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: the RAINBOW analysis. Ann Oncol. 2015; 26:2107-13.
49. Lee JL, Kim MK, Park I, et al. RandomizEd phase II trial of Sunitinib four weeks on and two weeks off versus Two weeks on and One week off in metastatic clear-cell type REnal cell carcinoma: RESTORE trial. Ann Oncol. 2015; 26:2300-5.
50. Hoffmann C, Leitz MR, Oberdorf-Maass S, et al. Comparative pharmacology of human beta-adrenergic receptor subtypes--characterization of stably transfected receptors in CHO cells. Naunyn Schmiedebergs Arch Pharmacol. 2004; 369:151-9.

51. Young R1, Glennon RA. S(-)Propranolol as a discriminative stimulus and its comparison to the stimulus effects of cocaine in rats. Psychopharmacology (Berl). 2009; 203:369-82.
52. Hoyer D, Clarke DE, Fozard JR, et al. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin). Pharmacol Rev. 1994; 46:157-203.
53. Available from: https://www.drugs.com/pro/propranolol-tablets.html, accessed on 22 May 2017.
54. Shand DG. Pharmacokinetics of propranolol: a review. Postgrad Med J. 1976; 52 Suppl 4:22-25.
55. Bowman SL, Hudson SA, Simpson G, et al. A comparison of the pharmacokinetics of propranolol in obese and normal volunteers. Br J Clin Pharmacol. 1986; 21:529-32.
56. Leahey WJ, Neill JD, Varma MPS, et al. Comparison of the efficacy and pharmacokinetics of conventional propranolol and a long acting preparation of propranolol. Br J Clin Pharmacol. 1980; 9:33-40.
57. Available from: http://www.mhra.gov.uk/spc-pil/?subsName=PROPRANOLOL%20HYDROCHLORIDE&pageID=SecondLevel, accessed on 22 May 2017.
58. Coelho M, Moz M, Correia G, et al. Antiproliferative effects of β-blockers on human colorectal cancer cells. Oncol Rep. 2015; 33:2513-20.
59. Schuller HM, Cole B. Regulation of cell proliferation by beta-adrenergic receptors in a human lung adenocarcinoma cell line. Carcinogenesis. 1989; 10:1753-5.
60. Lin X, Luo K, Lv Z, et al. Beta-adrenoceptor action on pancreatic cancer cell proliferation and tumor growth in mice. Hepatogastroenterology. 2012; 59:584-8.
61. Bernabé DG, Tamae AC, Biasoli ÉR, et al. Stress hormones increase cell proliferation and regulates interleukin-6 secretion in human oral squamous cell carcinoma cells. Brain Behav Immun. 2011; 25:574-83.
62. Valles SL, Benlloch M, Rodriguez ML, et al. Stress hormones promote growth of B16-F10 melanoma metastases: an interleukin 6- and glutathione-dependent mechanism. J Transl Med. 2013; 11:72.
63. Işeri OD, Sahin FI, Terzi YK, et al. beta-Adrenoreceptor antagonists reduce cancer cell proliferation, invasion, and migration. Pharm Biol. 2014; 52:1374-81.
64. Lang K, Drell TL 4th, Lindecke A, et al. Induction of a metastatogenic tumor cell type by neurotransmitters and its pharmacological inhibition by established drugs. Int J Cancer. 2004; 112:231-8.
65. Sood AK, Bhatty R, Kamat AA, et al. Stress hormone-mediated invasion of ovarian cancer cells. Clin Cancer Res. 2006; 12:369-75.
66. Yang EV, Sood AK, Chen M, et al. Norepinephrine up-regulates the expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in nasopharyngeal carcinoma tumor cells. Cancer Res. 2006; 66:10357-64.
67. Guo K, Ma Q, Wang L, et al. Norepinephrine-induced invasion by pancreatic cancer cells is inhibited by propranolol. Oncol Rep. 2009; 22:825-30.
68. Liao X, Che X, Zhao W, et al. The β-adrenoceptor antagonist, propranolol, induces human gastric cancer cell apoptosis and cell cycle arrest via inhibiting nuclear factor κB signaling. Oncol Rep. 2010; 24:1669-76.

69. Moretti S, Massi D, Farini V, et al. β-adrenoceptors are upregulated in human melanoma and their activation releases pro-tumorigenic cytokines and metalloproteases in melanoma cell lines. Lab Invest. 2013; 93:279-90.
70. Barbieri A, Bimonte S, Palma G, et al. Int J Oncol. 2015; 47:527-34. The stress hormone norepinephrine increases migration of prostate cancer cells in vitro and in vivo. Int J Oncol. 2015; 47:527-34.
71. Thaivalappil S, Bauman N, Saieg A, et al. Propranolol-mediated attenuation of MMP-9 excretion in infants with hemangiomas. JAMA Otolaryngol Head Neck Surg. 2013; 139:1026-31.
72. Zhang J, Deng YT, Liu J, et al. Norepinephrine induced epithelial-mesenchymal transition in HT-29 and A549 cells in vitro. J Cancer Res Clin Oncol. 2016; 142:423-35.
73. Wilson JM, Lorimer E, Tyburski MD, et al. β-Adrenergic receptors suppress Rap1B prenylation and promote the metastatic phenotype in breast cancer cells. Cancer Biol Ther. 2015; 16:1364-74.
74. Campbell JP, Karolak MR, Ma Y, et al. Stimulation of host bone marrow stromal cells by sympathetic nerves promotes breast cancer bone metastasis in mice. PLoS Biol. 2012; 10:e1001363.
75. Wolter JK, Wolter NE, Blanch A, et al. Anti-tumor activity of the beta-adrenergic receptor antagonist propranolol in neuroblastoma. Oncotarget. 2014; 5:161-72.
76. Wolter NE, Wolter JK, Enepekides DJ, et al. Propranolol as a novel adjunctive treatment for head and neck squamous cell carcinoma. J Otolaryngol Head Neck Surg. 2012; 41:334-44.
77. Albiñana V, Villar Gómez de Las Heras K, Serrano-Heras G, et al. Propranolol reduces viability and induces apoptosis in hemangioblastoma cells from von Hippel-Lindau patients. Orphanet J Rare Dis. 2015; 10:118.
78. Thaker PH, Han LY, Kamat AA, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nat Med. 2006; 12:939-44.
79. Annabi B, Lachambre MP, Plouffe K, et al. Propranolol adrenergic blockade inhibits human brain endothelial cells tubulogenesis and matrix metalloproteinase-9 secretion. Pharmacol Res. 2009; 60:438-45.
80. Park SY, Kang JH, Jeong KJ, et al. Norepinephrine induces VEGF expression and angiogenesis by a hypoxia-inducible factor-1α protein-dependent mechanism. Int J Cancer. 2011; 128:2306-16.
81. Ramu A, Spanier R, Rahamimoff H, et al. Restoration of doxorubicin responsiveness in doxorubicin-resistant P388 murine leukaemia cells. Br J Cancer. 1984; 50:501-7.
82. Pasquier E, Ciccolini J, Carre M, et al. Propranolol potentiates the anti-angiogenic effects and anti-tumor efficacy of chemotherapy agents: implication in breast cancer treatment. Oncotarget. 2011; 2:797-809.
83. Kanemi O, Zhang X, Sakamoto Y, et al. Acute stress reduces intraparenchymal lung natural killer cells via beta-adrenergic stimulation. Clin Exp Immunol. 2005; 139:25-34.
84. Kalinichenko VV, Mokyr MB, Graf LH Jr, et al. Norepinephrine-mediated inhibition of antitumor cytotoxic T lymphocyte generation involves a beta-adrenergic receptor mechanism and decreased TNF-alpha gene expression. J Immunol. 1999; 163:2492-9.
85. Khalili A, Hassan ZM, Shahabi S, et al. Long acting propranolol and HSP-70 rich tumor lysate reduce tumor growth and enhance immune response against fibrosarcoma in Balb/c mice. Iran J Immunol. 2013; 10:70-82.

86. Chang PY, Huang WY, Lin CL, et al. Propranolol Reduces Cancer Risk: A Population-Based Cohort Study. Medicine (Baltimore). 2015; 94:e1097.
87. Nkontchou G, Aout M, Mahmoudi A, et al. Effect of long-term propranolol treatment on hepatocellular carcinoma incidence in patients with HCV-associated cirrhosis. Cancer Prev Res (Phila). 2012; 5:1007-14.
88. Barron TI, Connolly RM, Sharp L, et al. Beta blockers and breast cancer mortality: a population-based study. J Clin Oncol. 2011; 29:2635-44.
89. Pasquier E, André N, Street J, et al. Effective Management of Advanced Angiosarcoma by the Synergistic Combination of Propranolol and Vinblastine-based Metronomic Chemotherapy: A Bench to Bedside Study. EBioMedicine. 2016; 6:87-95.
90. Bhattacharyya GS, Ranade A, Malhotra H, et al. Continuous metronomic temozolamide with propranolol and etodolac in recurrent globlastoma: A pilot study. J Clin Oncol. 2014; 32 suppl; abstr e13005.
91. Bhattacharyya GS, Babu KG, Bondarde SA, et al. Effect of coadministered beta blocker and COX-2 inhibitor to patients with pancreatic cancer prior to receiving albumin-bound (Nab) paclitaxel. J Clin Oncol. 2015; 33 suppl 3; abstr 302.
92. Lindgren ME, Fagundes CP, Alfano CM, et al. Beta-blockers may reduce intrusive thoughts in newly diagnosed cancer patients. Psychooncology. 2013; 22:1889-94.
93. Sethuraman G, Yenamandra VK, Gupta V. Management of infantile hemangiomas: current trends. J Cutan Aesthet Surg. 2014; 7:75-85.
94. Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics. 2013; 131:128-40.
95. Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. Pediatrics. 2011; 128:e259-66.
96. Deng GH, Liu J, Zhang J, et al. Exogenous norepinephrine attenuates the efficacy of sunitinib in a mouse cancer model. J Exp Clin Cancer Res. 2014; 33:21.
97. Liu J, Deng GH, Zhang J, et al. The effect of chronic stress on anti-angiogenesis of sunitinib in colorectal cancer models. Psychoneuroendocrinology. 2015; 52:130-42.
98. Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. Stat Med. 2005; 24:3089-110.

Appendix A: Schedule of Assessments

The schedule of required assessments is presented in this appendix. Assessments for safety and patient reported outcomes are to occur corresponding with study which are fixed from Week 1 Day 1 (W1D1) defined as the date of the first dose of study treatment. In the absence of toxicity, all scheduled safety visits should occur within ± 2 days of the nominal time, unless otherwise indicated. Unscheduled safety assessments are to be performed weekly (or more frequently as clinically indicated). Other unscheduled visits or assessments are permitted whenever necessary.

Appendix A: Schedule of Assessments

	Pre-treatment period	Treatment period								Postdiscontinuation period	
Assessment	Screening (≤ 7 days)	W1D1[5]	W2D1	W3D1	W7D1	W13D1	W19D1	W25D1	After beginning of W25	End-of-treatment visit	Follow-up
Informed consent	X										
Inclusion/exclusion criteria	X										
Medical history	X	X	X	X	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	X	X	X[3]	X	
Vital signs	X	X	X	X	X	X	X	X	X[3]	X	
Performance status	X	X	X	X	X	X	X	X	X[3]	X	
ECG	X		X	X	X	X	X	X	X[3]	X	
24-hour Holter ECG monitoring	X									X	
Echocardiography	X									X	
Cardiology consultation	X		X[2]	X[2]	X					X	
Hematology	X				X	X	X	X	X[3]	X	
Biochemistry	X				X	X	X	X	X[3]	X	
Coagulation	X									X	
Urine analysis	X										
β-HCG, HIV tests	X										
CT/MRI	X[1]					X		X	X[4]		
Bone scan[1,2]	X[1,2]										
Tumour tissue samples[6]	X										
Serum biomarkers	X				X					X	
EORTC QLQ-C30, FKSI-15, PSS questionnaires		X			X	X	X	X	X[3]	X	
Sunitinib and propranolol administration record		Since the first day of sunitinib/propranolol administration up to the end-of-treatment visit									
Blood pressure and pulse home monitoring (twice daily)		Since the first day of sunitinib/propranolol administration up to the end-of-treatment visit									
Adverse events		Since the first day of sunitinib/propranolol administration up to the end-of-treatment visit									
Dispense/return of study drugs		X	X	X	X	X	X	X	X	X	
Further cancer treatment and survival status											Every 8 weeks (±7 days) until the end of study or death

[1] ≤ 28 days, [2] if clinically indicated, [3] every 6 weeks, [4] every 12 weeks, [5] prior to first dose of sunitinib/propranolol, [6] whenever available

Appendix B: Karnofsky Performance Status (KPS) Scale

100 – Normal; no complaints; no evidence of disease.

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 to do active work.

60 – Requires occasional assistance, but is able to care for most of their personal needs.

50 – Requires considerable assistance and frequent medical care.

40 – Disabled; requires special care and assistance.

30 – Severely disabled; hospital admission is indicated although death not imminent.

20 – Very sick; hospital admission necessary; active supportive treatment necessary.

10 – Moribund; fatal processes progressing rapidly.

0 – Dead

Appendix C: Memorial Sloan Kettering Cancer Center (MSKCC) Criteria

Criterion	Points
Karnofsky performance status ≤ 70%	(No - 0; Yes - 1)
Time from diagnosis to treatment < 1 year	(No - 0; Yes - 1)
Hemoglobin concentration < LLN	(No - 0; Yes - 1)
Serum corrected calcium concentration > 10 mg/dl (> 2.5 mmol/L)	(No - 0; Yes - 1)
Lactate dehydrogenase level > 1.5x ULN	(No - 0; Yes - 1)

Favorable risk group: 0 points.
Intermediate risk group: 1-2 points.
Poor risk group: 3-5 points.

Appendix D: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Definitions

Baseline: Baseline is defined as the most recent assessment performed prior to initiation of study treatment.

Baseline assessments must be performed within the period defined in the protocol.

Measurable lesions: Except for lymph nodes as described below, measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan (if CT scans have slice thickness greater than 5 mm the minimum size for a measurable lesion is twice the slice thickness).

• To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and recorded.

• MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Nonmeasurable lesions: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥10 to < 15 mm short axis), are considered nonmeasurable. Lymph nodes that have a short axis < 10 mm are considered nonpathological and are not be recorded or followed. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/ pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as nonmeasurable.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as target lesions and measured and recorded at baseline. Target lesions are to be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. Target lesions will be measured at each assessment (longest axis for nonnodal lesions, shortest axis for measurable malignant nodal lesions).

Nontarget lesions: All other lesions (or sites of disease) including all non-measurable lesions (including pathological lymph nodes with ≥ 10 to <15 mm short axis) and all measurable lesions over and above the 5 target lesions are to be identified as non-target lesions and recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each is to be recorded throughout follow-up. Lymph nodes that have a short axis < 10mm are considered non-pathological and are not to be recorded or followed.

To be considered progression of non-target lesions in the presence of measurable disease, unequivocal progression is defined as substantial worsening in non-target disease such that, even in

the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of the therapy.

Special Consideration

Lesions by clinical examination will not be used for response in this study.

Cystic lesions

• Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) 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.

Bone lesions

• Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

• Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

• Blastic bone lesions are non-measurable.

Lesions with prior local treatment

• Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable.

Imaging Methods

The same method of assessment and the same technique used to characterize each identified and reported lesions at baseline should be used during each follow-up assessment. All measurements should be taken and recorded in metric notation using a ruler or calipers. Imaging based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but assessed by clinical examination (referring to biopsy-proven visible lesion(s) on the chest).

Chest x-ray: Chest x-ray will not be used for response assessment in this study.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion is twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scan) except for lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences

used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Positron emission tomography will not be used for response assessment in this study.
Ultrasound: Ultrasound will not be used for response assessment in this study.
Bone scans will be used to assess the presence or disappearance of the bone component of bone lesions. CT or MRI scan will be used to confirm ambiguous results of bone scans. Preferred method for confirmation is MRI.

Time Point Assessments

The frequency and schedule of tumor assessments is defined in the protocol. The schedule is to be maintained regardless of whether study treatment is held or discontinued. At baseline, tumors and lymph nodes are classified and documented as target or nontarget per the definitions provided above. It is possible to record multiple nontarget lesions involving the same organ as a single item (eg, 'multiple liver metastases'). At all postbaseline (follow-up) evaluations the baseline classification (target, nontarget) is to be maintained and lesions are to be documented and described in a consistent fashion over time (eg, recorded in the same order on source documents). At each assessment, a sum of the diameters (longest for nonnodal lesions, short axis for nodal lesions) for all target lesions will be calculated and included in source documents. The baseline sum of the diameters (SoD) will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. The lowest SoD (nadir) since (and including) the baseline value will be used as reference for evaluating progression.
After baseline, target lesions should have the actual size documented, if possible, even if the lesions become very small. If in the opinion of the radiologist the lesion has likely disappeared, 0 mm should be recorded. If the lesion is present but too small to measure, an indicator for 'too small to measure' this should be included in source documents.
For target lesions, measurements should be taken and recorded in metric notation. All tumor measurements must be recorded in millimeters.
Nontarget lesions are to be assessed qualitatively (present, resolved, or unequivocal progression) and new lesions, if any, are to be documented separately.
At each evaluation, progression status is to be determined based upon the time point status for target lesions, nontarget lesions, and new lesions.
Finding of new lesions should not be attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. Necrosis of preexisting lesions as part of a response to treatment should be excluded before defining a 'new' cystic lesion. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion. If a new lesion is equivocal because of its small size, repeat

scans need to confirm there is definitely a new lesion, and progression should be declared using the date of the initial scan.

Time point progression can be based solely on bone scans if there is unequivocal evidence of new bone scan lesions. New bone scan lesions will be considered malignant in the absence of correlative imaging or clinical data that demonstrate lesions are not malignant. Follow up imaging may be required to ensure new lesions are unequivocal. Increases in the density or size of bone scan lesions present at baseline cannot be the basis of progression.

Time point response (TPR) criteria

Target Lesion TPR

Complete Response (CR) - Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR) - At least a 30% decrease in SoD of target lesions, taking as a reference the baseline SoD

Stable Disease (SD) - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive Disease (PD) - At least a 20% increase in the SoD of target lesions, taking as a reference the smallest (nadir) SoD since (and including) baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.

Not Applicable (NA) - No target lesion identified at baseline.

Unable to Evaluate (UE) - One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criterion for PD.

Non-Target Lesion TPR

Complete Response (CR) - Disappearance of all non-target lesions. All lymph nodes must be nonpathological in size (<10 mm short axis)

Non-CR / Non-PD - Persistence of one or more non-target lesion(s).

Progressive Disease (PD) - Unequivocal progression of non-target lesions. Unequivocal progression should normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase

Not Applicable (NA) - No non-target lesions identified at screening

Unable to Evaluate (UE) - One or more non-target lesions are not imaged and the remaining nontarget lesions do not meet the criterion for PD.

New Lesion TPR

Yes - Lesion present at follow-up visit either for the very first time or reappearing (ie, lesion was present at baseline, disappeared at a follow-up visit and re-appeared later). On bone scan, a single new lesion may not

be sufficient to qualify as PD. Confirmation should be obtained by performing CT or MRI of the area of concern to confirm ambiguous results of bone scan. Preferred method for confirmation is MRI.

No - No new lesions present at follow-up.

Unable to Evaluate (UE) - Subject not assessed or incompletely assessed for new lesions.

Evaluation of Overall Time Point Response

Target Lesion TPR	Non-target Lesion TPR	New Lesion TPR	Overall TPR
CR	CR or NA	No	CR
CR	Non-CR/non-PD	No	PR
CR	UE	No	PR
PR	Non-PD or NA or UE	No	PR
SD	Non-PD or NA or UE	No	SD
UE	Non-PD	No	UE
PD	Any	No or Yes or UE	PD
Any	PD	No or Yes or UE	PD
Any	Any	Yes	PD
NA	CR	No	CR
NA	Non-CR/Non-PD	No	Non-Cr/Non-PD
NA	UE	No	UE
Non-PD	Non-PD	UE	UE

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease, UE, unable to evaluate; NA, not applicable (no such lesions at screening); Any, CR, PR, SD, PD, NA, or UE.

Appendix E: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 Version 3)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix F: FACT-Kidney Symptom Index - 15 (FKSI-15) Questionnaire

FKSI -15

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I have pain	0	1	2	3	4
C 2	I am losing weight	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
GP3	I am able to enjoy life	0	1	2	3	4
B 1	I have been short of breath	0	1	2	3	4
GB6	I worry that my condition will get worse	0	1	2	3	4
C 6	I have a good appetite	0	1	2	3	4
L 2	I have been coughing	0	1	2	3	4
BB8	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
GP1	I am able to work (include work at home)	0	1	2	3	4
KC12	I have had blood in my urine	0	1	2	3	4
GP5	I am sleeping well	0	1	2	3	4

Appendix G: The Perceived Stress Scale (PSS) Questionnaire

PERCEIVED STRESS SCALE

The questions in this scale ask you about your feelings and thoughts during the last month. **In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.**

Name _____ Date _____

Age _____ Gender (*Circle*): **M F** Other _____

0 = Never 1 = Almost Never 2 = Sometimes 3 = Fairly Often 4 = Very Often

1. In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5. In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last month, how often have you been able to control irritations in your life?	0	1	2	3	4
8. In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4