Study Type	Open-label, randomized, observational phase III study
Coordinating investigator (LKP)	Prof. Dr. med. Viktor Grünwald Univ.-Prof. für interdisziplinäre Uroonkologie Westdeutsches Tumorzentrum Innere Klinik (Tumorforschung) und Klinik für Urologie Universitätsklinikum Essen, Hufelandstr. 55 45147 Essen Telefon: +49 0201-723 85584 E-Mail: Viktor.Gruenwald@uk-essen.de
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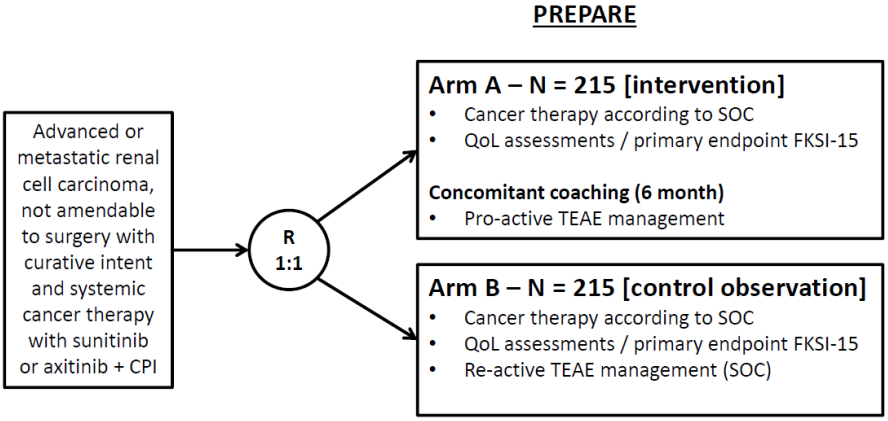
Objectives	Primary objective: To determine the impact of a 24 weeks concomitant coaching on patient reported outcomes of patients receiving standard first-line treatment for mRCC with sunitinib or a combination of checkpoint inhibitor (CPI) + axitinib. Secondary objectives: Assessment of the impact of a 24 weeks concomitant coaching on additional QoL measures, patient compliance, efficacy and safety. Exploratory objectives: Assessment of inflammatory markers in tumor samples and serum.
Endpoints	Primary endpoint: QoL assessment during sunitinib treatment: Rate of responders to concomitant coaching assessed by the FKSI-15 questionnaire Secondary endpoints: • ORR according to RECIST 1.1 criteria • OS • PFS • Duration of treatment • Dose density of sunitinib • Rate of hospitalization irrespective of TEAEs • Treatment beyond progression • Further cancer treatment and time to first subsequent therapy (TFST) • Patient adherence / drug-related treatment discontinuation rates: percentage of patients with treatment discontinuation due to specific ADRs (e.g. hand-foot syndrome, diarrhea, stomatitis, fatigue, hypertension) • Treatment Emergent Adverse Events according to CTC 4.03: • Frequency/incidence, severity, percentage reduction, time-to-event of ADRs, SAEs and specific TEAEs (e.g. hand-foot syndrome, diarrhea, stomatitis, fatigue, hypertension) • Reduction of grade 3/4 ADRs • Health related Quality of Life (FACT-G, EQ-5D) • Time to improvement or deterioration measured by HRQoL • Assessment of comorbidities by Charlson Comorbidity Index (CCI) and social status
Number of patients	N=430 total Currently recruited: **48**

Start date	Q1/2017
More centres?	Target number: 100 / Yes (currently **35** sites participating)
Key inclusion criteria	**1.** Written informed consent and any locally required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations. **2.** Age ≥ 18 years at time of study entry. **3.** Advanced or metastatic renal cell carcinoma, not amendable to surgery with curative intent, rendering the patient eligible for 1st-line systemic treatment. **4.** Intended first-line treatment with sunitinib, with pembrolizumab plus axitininb or with avelumab plus axitinib. **5.** Documented progressive disease within 6 months prior to study inclusion. **6.** Patients with measurable disease (at least one unidimensionally measurable target lesion by CT-scan or MRI) according to modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and non-measurable disease are eligible. **7.** Prior radiotherapy and surgery are allowed if completed 4 weeks (for minor surgery and palliative radiotherapy for bone pain: 2 weeks) prior to start of treatment and patient recovered from toxic effects. **8.** Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry. 9. Subject is willing to receive additional concomitant coaching and able to comply with the QoL/PRO assessments specified in the protocol for the duration of the study including scheduled visits, examinations and follow up.
Key exlusion criteria	**1.** Any other anti-cancer treatment aside of sunitinib, axitinib, pembrolizumab and avelumab for mRCC (except palliative radiotherapy). **2.** Previous malignancy (other than mRCC) which either progresses or requires active treatment. Exceptions are: basal cell cancer of the skin, pre-invasive cancer of the cervix, T1a or T1b prostate carcinoma, or superficial bladder tumor [Ta, Tis and T1]. **3.** CNS metastases, unless local therapy has been for at least 3 month and patient does not require the use of steroids. **4.** Chronic liver disease with Child-Pugh B or C score **5.** Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year). **6.** Any condition that, in the opinion of the investigator, would interfere with evaluation of the concomitant coaching or QoL assessments or interpretation of patient safety or study results. **7.** Participation in another clinical study with an investigational product during the last 30 days before inclusion. **8.** Any previous treatment with a tyrosine kinase inhibitor or checkpoint inhibitor for metastatic disease. Adjuvant or neoadjuvant therapy for localized disease is permitted, provided that relapse occurred at least 6 months after last exposure. **9.** Previous enrollment or randomization in the present study (does not include screening failure). **10.** Involvement in the planning and/or conduct of the study (applies to both Pfizer staff and/or staff of sponsor and study site). **11.** Patient who might be affiliated or otherwise dependent on the sponsor, site or the investigator. **12.** Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities [§ 40 Abs. 1 S. 3 Nr. 4 AMG].

	13. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].

Scheme of therapy	Cancer treatment
	
	Standard treatment of mRCC according to the prescribing information of
	
	• sunitinib: recommended dosage is 50 mg sunitinib once daily for 4 weeks followed by 2 weeks offtreatment [4/2 schedule; total cycle length = 6 weeks].
	or
	• avelumab: recommended dose of avelumab incombination with axitinib is 800 mg administered intravenously over 60 minutes every 2 weeks and recommended dose of axitinib 5 mg orally taken twice daily.
	or
	• pembrolizumab: recommended dose of pembrolizumab as part of combination therapy is 200 mg every 3 weeks administered as an intravenous infusion over 30 minutes and recommended dose of axitinib is 5 mg orally taken twice daily.
	
	Cancer treatment management, dosage, dose modifications (in particular schedule adjustments during therapy) and concomitant treatment and medication are at the discretion of the treating physician.
	
	Concomitant coaching [primary intervention]:
	The corner stones of the pro-active coaching are as follows:
	• Patient education
	  ○ Information on nature and severity of treatment emergent AEs
	  ○ Information about remedies for TEAEs
	  ○ Propagation and explanation of tests and treatment decisions
	  ○ Patient instruction on self-care and preventive measures
	
	• Preemptive AE treatment strategies
	  ○ Proactive assessment of treatment emergent AEs with emphasis on predefined ADRs of special interest (fatigue, diarrhea, stomatitis, skin toxicities, hypertension)
	• Supervision of reported ADR severity, ADR mitigation strategies and cancer treatment modification by treating physician
	• Therapy surveillance by phone with a structured interview (week 1, 2, 3, 4, 5 during first 2 cycles; week 2 and 4 in subsequent cycles)
	• Availability of coach for unscheduled contacts by phone (during normal business hours)

	
Criteria for tumor evaluation	RECIST 1.1
Rationale	Clinical outcome has improved since the introduction of targeted therapies and the recent addition of immune-checkpont inhibitors in the field of metastatic renal cell carcinoma (mRCC). Agents inhibiting the vascular endothelial growth factor receptor (VEGFR) are a key element in the treatment of mRCC. Sunitinibis associated with a response rate of approx. 30% (Motzer et al., 2013). However, 10-20% of patients are not able to tolerate treatment and stop early because of treatment-related toxicity (Motzer et al., 2013; 2007). For patients dropping-off therapy for intolerance, clinical outcome remains poor (Grünwald et al., 2013). Recently, new 1st-line treatment strategies for advanced RCC combining the VEGFR inhibitor axitinib with immune checkpoint inhibitors (CPI) have emerged. Results of the Javelin renal 101 trial demonstrate that treatment efficacy of the avelumab + axitinib combination was superior to that of sunitinib, while toxicity profiles of the two regimens are very similar in terms of adverse event types and incidence (Motzer et al., 2019). Similar results have been reported for the combination of pembrolizumab + axitinib from the Keynote-426 study (BI et al., 2019). As single agent CPI therapies have become a routine treatment in several tumor entities in recent years, immune-related adverse events (irAE) have become a part ofclinical reality. But importantly, irAE require management strategies that differ from AE caused by TKIs. When combining CPI with axitinib, the overlap of toxicities between both may mask irAE and may lead to delayed management, thereby furthering the risk of severe toxicity. Proactive treatment has been shown to impact time to event and severity of adverse events (AE) in cancer patients treated by EGFR inhibition plus chemotherapy (Lacouture et al., 2010), justifying a structured approach to manage treatment-emergent adverse events (TEAEs) proactively. To date, prospective data for management of irAE is scarce, but type and severity of TEAEs render a proactive intervention of putative benefit. The goal of our study is to define the benefit of proactive coaching in mRCC, when compared to a reactive approach, which is considered the standard of care. It´s hypothesized that intensified proactive coaching during the first 24 weeks of treatment improves patients' health related quality of life (HR-QoL), which may improve patients' adherence to treatment and ultimately clinical outcome.