Clinical Research Platform On Renal Cell Carcinoma Treatment And Outcome (CARAT)

Authors

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Steering Board
## Addresses and responsibilities

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<th>Full Form</th>
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<tr>
<td>EDC</td>
<td>Electronic data capture</td>
</tr>
<tr>
<td>e. g.</td>
<td>For example</td>
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<tr>
<td>FACT</td>
<td>Functional Assessment of Cancer Therapy</td>
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<tr>
<td>FPI</td>
<td>First patient in</td>
</tr>
<tr>
<td>FPFV</td>
<td>First patient first visit</td>
</tr>
<tr>
<td>FU</td>
<td>Follow up</td>
</tr>
<tr>
<td>HRQOL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>LPI</td>
<td>Last patient in</td>
</tr>
<tr>
<td>LPO</td>
<td>Last patient out</td>
</tr>
<tr>
<td>mTOR</td>
<td>Mammalian target of rapamycin</td>
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<tr>
<td>PFS</td>
<td>Progression free survival</td>
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<tr>
<td>PRO</td>
<td>Patient-reported outcome</td>
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<tr>
<td>QLQ</td>
<td>Quality of Life Questionnaire</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RCC, mRCC</td>
<td>Renal Cell Carcinoma, locally advanced, inoperable or metastatic RCC</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>TKI</td>
<td>Tyrosine Kinase Inhibitor</td>
</tr>
<tr>
<td>VEGF(R)</td>
<td>Vascular endothelial growth factor (receptor)</td>
</tr>
<tr>
<td>VHL</td>
<td>Von-Hippel Lindau (protein)</td>
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# Project plan summary

<table>
<thead>
<tr>
<th><strong>Project Title</strong></th>
<th><strong>Clinical Research Platform On Renal Cell Carcinoma Treatment And Outcome (CARAT)</strong></th>
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<tbody>
<tr>
<td><strong>Study Type</strong></td>
<td>National, observational, open, prospective, longitudinal, multicenter cohort study</td>
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<tr>
<td><strong>Population</strong></td>
<td>Adult patients with mRCC requiring systemic treatment intervention.</td>
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<tr>
<td><strong>Study treatment and follow-up</strong></td>
<td>Routine care as per site standard / Physician's choice according to patient's need.</td>
</tr>
<tr>
<td><strong>Number of patients, number/specification of sites</strong></td>
<td>1,000 patients with mRCC Up to 500 of these patients will participate in the additional module &quot;Patient-reported Outcomes&quot;.</td>
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<tr>
<td><strong>Purpose and rationale</strong></td>
<td>Around 16,000 kidney cancer diagnoses are estimated for 2016 in Germany. Almost one third of the patients with RCC already present with advanced disease at diagnosis. The treatment and outcome of mRCC has markedly improved over the last decade with the introduction of molecular agents that target tyrosine kinase signaling including VEGFR (VEGF receptor) signaling (sunitinib, sorafenib, pazopanib, lenvatinib and cabozantinib, bevacizumab), PI3K-AKT-mTOR signaling (temsirolimus and everolimus), and recently PD-1 (programmed death-1) signaling (nivolumab). Systematic, prospective, longitudinal cohort studies provide data on patients in routine practice where patients' sociodemographic and clinical characteristics often differ from those treated in randomized controlled trials. The CARAT clinical research platform will continue the data collection from the Tumor Registry Renal Carcinoma, started in 2008, and provide real world data on treatment reality from all sectors in Germany. It will show if and how the choice of treatment changes over time and how outcome results from clinical trials translate into routine care. Associated modules will investigate patient-reported outcomes and set up a decentralized biobank for future translational analyses.</td>
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| **Objectives** | - To describe treatment reality (systemic treatment and sequential treatments) applied in German real-life practice.  
- To describe patient and tumor characteristics in routine care.  
- To describe physician-reported factors affecting treatment decision making.  
- To assess effectiveness of systemic treatment with immunotherapy, anti-angiogenesis, mTOR or checkpoint inhibitors by various outcome parameters such as response rate, progression-free survival, overall survival.  
- To assess effectiveness of sequential treatment strategies.  
- To identify parameters affecting prognosis. |
To assess use of selected supportive therapies.
  - Module Patient-Reported Outcomes (PROs): To evaluate health-related quality of life (QoL) and symptom burden
  - Module Biomarker Profiling: To establish a decentralized biobank for future investigational scientific biomarker testing

### Inclusion criteria
- Female and male patients with mRCC (locally advanced, inoperable or metastatic)
- Patients at start of their first-line systemic treatment for mRCC
- Written informed consent
  - Patients participating in the PRO module: signing of informed consent form and completion of baseline questionnaire before start of initial systemic treatment
  - Patients not participating in the PRO module: within twelve weeks after start of systemic first-line for mRCC
- Age ≥ 18 years
- Patients participating in the PRO module: Sufficient knowledge of the German language to fill-in the questionnaires

### Exclusion criteria
- Patients with prior systemic therapy for mRCC
- No systemic treatment for mRCC

### Data collection
Data are collected from medical files and patient’s records, and transferred into an electronic documentation system (EDC).
Baseline (demographic, clinical, tumor) characteristics, treatment decision making, molecular testing, all systemic treatments, selected supportive therapies, outcome (response, progression, survival), course of disease will be documented.

### Patient-reported outcomes
Participation of patients in the PRO module is optional.
PROs will be assessed using the NCCN-FACT FKS1-19 questionnaire and additional items addressing health-related quality of life and symptom burden in patients with kidney cancer. 500 patients will be asked to fill-in questionnaires before start of treatment, and then every 3 months for a maximum of 2 years.

### Molecular testing
Patients will be asked to give additional informed consent agreeing that tumor samples taken during routine treatment can be used for further scientific testing.
For the decentralized biobank, pathological material will remain with the local pathologist.

### Statistics
Descriptive analyses will be performed annually.

### Planned Timelines
- First Patient In (FPI/FPFV): Q4 / 2017
- Last Patient In (LPI): Q4 / 2021
- Last Patient Out (LPO) + Survival Update: Q4 / 2024

### Contact details
- Sponsor:
- Project Lead:
1. Background

1.1. Epidemiology

Around 16,000 kidney cancer diagnoses are estimated for 2016 in Germany (1). Renal cell carcinoma (RCC) accounts for 85% of all malignant tumors of the kidney (2). Almost one third of the patients already presents with advanced disease (T3-4), lymph node infiltration or metastases at diagnosis (3). Clear cell carcinoma accounts for more than 80% of all RCCs (3) with most cases showing decreased levels of VHL (Von Hippel-Lindau) protein and consequently overexpression of proliferation-promoting and angiogenesis-inducing factors, including VEGF (vascular endothelial growth factor) (4).

1.2. Treatment

The treatment of mRCC has markedly improved over the last years with the introduction of molecular agents that target PI3K-AKT-mTOR signaling, VEGFR (VEGF receptor) signaling, and recently PD-1 (programmed death-1) signaling. Several tyrosine kinase inhibitors (TKIs), and several mammalian target of rapamycin (mTOR) inhibitors targeting the PI3K-ATK-mTOR signaling pathway have been approved over the last decade for the treatment of mRCC: the TKIs sunitinib and sorafenib in 2006, followed by mTOR inhibitors temsirolimus and everolimus in 2007 and 2009, the TKIs pazopanib in 2010 and axitinib in 2012, and recently lenvatinib and cabozantinib in 2016. Besides TKIs, targeting the PI3K-AKT-mTOR pathway has been shown to decrease VEGF secretion. In addition, the anti-VEGF antibody bevacizumab applied in combination with Interferon alpha was approved in 2008 and widened the agents targeting the VEGF. Recently, with the approval of nivolumab, a PD-1 (programmed death-1) inhibitor antibody, in 2016 the therapeutic spectrum has widened once more. The launch of TKIs in 2006 significantly improved outcome of mRCC patients (5–7). Sunitinib and pazopanib are nowadays recommended as standard therapeutics in the first-line treatment of mRCC (2,3,8). Resistance to TKIs may be driven by adoption of alternative signaling pathways to compensate for the inhibition of VEGFR signaling and provide pro-survival stimulation. Application of other TKIs such as axitinib or sorafenib or the mTOR inhibitor everolimus are currently advised as second-line therapy in patients that progress on VEGFR TKIs in first line (2,3,8). However, two recently approved agents, cabozantinib and nivolumab, showed improved overall survival compared to everolimus in phase III trials with patients with prior treatment (10, 11) and present new options for pre-treated patients. The multikinase inhibitor cabozantinib targets VEGFR, MET and other receptor tyrosine kinases. Increasing evidence suggested a role of MET, a receptor for the hepatocyte growth factor, in resistance to TKIs (9). The “checkpoint” PD-1 inhibitor, nivolumab, restores therapeutic anti-tumoral immunity and offers an entirely novel therapeutic approach to treat mRCC (11). Finally, the multikinase inhibitor lenvatinib was recently approved in combination with everolimus after showing prolonged PFS in a phase II study in mRCC patients with prior VEGF-targeted therapy (11).

As more treatment options for RCC patients have become and will become available, there will be a wider variance of treatments applied to individual patients. This raises questions as to how fast newly approved treatments are applied in routine practice and how outcome results translate to patients outside of clinical trials. Efficacy of novel agents is established
based on randomized controlled trials (RCTs), which have to recruit a selected patient population to ensure a high degree of internal validity. Systematic, prospective, longitudinal cohort studies providing data on routine care are highly important to assess the state of care and complement the data generated from the pivotal clinical trials.

1.3. Treatment in routine practice in Germany

From 2008 till 2016, the Clinical Tumor Registry on advanced Renal Carcinoma, conducted by a network of about 250 German oncologists and urologists, has prospectively collected data on 1,500 outpatients with advanced renal cell carcinoma. All patients are followed until death or for a maximum of 3 years (12–16).

It could be shown that patients in routine care differ in their characteristics from those in randomized clinical trials and fewer than 50% would fulfil common trial inclusion criteria. The majority of patients, recruited since 2008, received TKI as first-line treatment. Median overall survival was 26.0 months for “trial-eligible” and 12.6 months for “trial-ineligible” patients (12). During the 8 years recruitment period, pazopanib followed by everolimus replaced sunitinib followed by sorafenib as the most frequently used sequential first-line-second-line treatment. The Body-Mass-Index was identified as a prognostic factors independent of the MSKCC score (15).

1.4. Quality of life

mRCC patients can be distressed by symptoms related to the tumor and to the anti-cancer treatment. Patient-reported outcomes (PRO) addressing health-related quality of life (QoL) and symptom burden are increasingly used in clinical trials to complement objective measurement parameters such as response and survival with subjective perception of the patient’s well-being.

Systematic data on PROs in routine practice are rare. A cross-sectional study of PROs from patients in the Tumor Registry Renal Cell Carcinoma found that perception of symptoms differs between patients and physicians, and that symptoms such as fatigue can affect overall quality of life. It was suggested that implementation of PROs into routine care could facilitate patient-physician communication and improve the quality of care (17,18).

Longitudinal assessments of PROs in patients treated in routine practice will allow identification of symptoms inadequately addressed by supportive care. It would also enable comparison of PROs between different (sequential) treatment strategies.

1.5. Biomarker testing

Treatment decision in mRCC is guided by general condition, comorbidities, and prognostic indices (19), however, the success of antiangiogenic drugs and immunotherapy could be increased by selecting patients most likely to respond to treatment. Biomarker testing in the past to search for predictive and prognostic biomarkers included interleukins, cytokines, VEGF, HIF-1a as well as VHL mutations. Of these, high VEGF expression, especially in endothelial cells, was identified as predictive for longer PFS in sorafenib-treated patients, single-nucleotide polymorphism variants in VEGFR as predictive of poor PFS with bevacizumab, expression levels of HIF-1a as predictive of response to pazopanib, and serum LDH as prognostic and predictive biomarker for survival of poor-risk patients treated with temsirolimus (20). However, none of these markers are established as tests prior to treatment deci-
sion making in clinical routine since precision of these markers did not improve prognostic accuracy of conventional prognostic scores. In addition, prognostic and predictive markers of response to novel kinase inhibitors and PD-L1 checkpoint inhibitor nivolumab are to be investigated. In the respective phase III trial, response was independent of PD-L1 expression levels (21). In conclusion, there is still a pressing need to identify predictive biomarkers that can be used to direct therapy decision making. Longitudinal observational cohort studies provide an ideal setting to collect tumor samples and connect epidemiological data on the course of disease with translational biomarker analysis.

2. Study rationale and purpose

The recent approval of novel treatments warrants an extension of the Tumor Registry Renal Cell Carcinoma. The CARAT clinical research platform will continue to provide real world data on treatment reality across all sectors in Germany.

The project will reveal how German mRCC patients starting treatment from 2017 onwards are treated in routine practice over the entire course of disease and how the approval of new treatments will change routine care. In addition, systematic and longitudinal collection of PROs will be used to assess QoL, symptom burden and state of care in real-life patients. The decentralized biobank will set up a national basis for future translational projects on molecular alterations.

3. Objectives

- To describe demographic and clinical characteristics of patients with mRCC requiring systemic treatment in routine care.
- To assess treatment and outcome of patients with mRCC requiring systemic treatment, in particular:
  o To describe systemic treatment and sequential treatments applied in German routine practice.
  o To describe physician-reported factors affecting treatment decision making.
  o To assess effectiveness of systemic treatment with immunotherapy, anti-angiogenesis, mTOR or checkpoint inhibitors by various outcome parameters such as response rate, progression free survival, overall survival.
  o To assess effectiveness of sequential treatment strategies.
  o To identify parameters affecting prognosis.
  o To assess use of selected supportive therapies.
- Module Patient-Reported Outcomes: To evaluate health-related quality of life and symptom burden
  o To correlate distinct PRO parameters with effectiveness of therapy.
  o To compare PRO parameters with regard to different treatment strategies.
- Module Biomarker Profiling: To establish a decentralized biobank for future investigational scientific biomarker testing.
4. Project design

4.1. Description of project design

The Renal Cell Carcinoma Research Platform is a national, prospective, longitudinal, multi-center cohort study with associated satellites.

1,000 patients with advanced renal cell cancer, previously untreated for their advanced disease, will be recruited at the start of first-line treatment in up to 150 study sites (urologists and oncologists from both, clinics and outpatient centers) in Germany. Treatment and course of disease for each patient will be observed and documented for three years.

After informed consent is obtained, data on patients’ demographic and clinical (tumor) characteristics, on molecular testing and prior treatments will be documented. Patients will be treated according to their physician’s choice based on patients’ individual needs and schedules. During the three year observation and documentation period of each patient, data on all treatments, course of disease and outcome will be updated at least every six months.

Timetable

Planned First Patient In (FPI) Q4/2017
Planned Last Patient In (LPI) Q4/2021
Planned Last Patient Out (LPO) + Survival Update Q4/2024

Figure 1: Project timetable
4.2. Module Patient-Reported Outcomes – PRO

Up to 500 patients will participate in the PRO module. Patients will be asked to complete the first PRO assessment at time of recruitment (before or at first day of systemic treatment). Afterwards, patients will receive PRO questionnaires every three months for a maximum of 24 months (2 years).

Figure 2: PRO assessment: timetable

4.3. Module Biomarker profiling - Decentralized biobank

All patients will be asked to give consent for their tumor sample to be used for future investigational translational research. If the patient agrees, the sample’s identification number will be documented together with contact details of the local pathology where the tumor sample is stored. For future translational research projects, tissue samples will be collected from local pathologists/molecular geneticists, shipped to a central pathology and analyzed for specific biomarkers. Translational research projects will be described in detail in independent research proposals.

Figure 3: Decentralized biobank
5. Recruitment

Study sites are asked to enroll all patients that meet the inclusion criteria consecutively without selecting by any means. Patients receive oral and written information about the study and are asked to give written informed consent in duplicate (one copy for the participant, one for the recruiting physician).

Patient's recruitment is completed by:

- Collecting written informed consent
- Registering patient in the electronic data capture (EDC) system
- If patient participates in the PRO satellite: Reporting the contact details (name, address) through the specific report form in the electronic system

The investigator or designee must ensure that only eligible patients are recruited into the project.

5.1. Inclusion criteria

Patient who meet all of the following criteria are eligible to participate in the project:

- Female and male patients with advanced renal cell carcinoma (mRCC), defined as metastatic or inoperable disease
- Patients at the start of their initial systemic treatment for mRCC
- Written informed consent
  - Patients participating in the PRO module: prior to or at start (first day) of systemic first-line treatment for mRCC
  - Patients not participating in the PRO module: within twelve weeks after start of systemic first-line treatment for mRCC
- Age ≥ 18 years
- Patients participating in the PRO module: Sufficient knowledge of the German language to fill-in the questionnaires

5.2. Exclusion criteria

- Patients with prior systemic therapy for mRCC
- Patient who do not receive any systemic therapy for mRCC

6. Study variables

6.1. Data collected in the electronic Case Report Form (eCRF)

- Patient characteristics e.g. year of birth, sex, height, weight, performance status, comorbidities
- Disease characteristics e.g. biomarkers, histology, TNMGR of primary tumor, prognostic factors (e.g. relevant to MSKCC score), location of metastases
- Factors affecting treatment decision making (physician questionnaire)
- Molecular testing of biomarkers
- Details on all previous and all subsequent systemic treatments including type of treatment, first and last application, dose and dose modifications
- Outcome (best response(s), date(s) of progression, date of death)
- Key details on surgery, such as date and location, prior to inclusion and during course of disease
- Key details on radiotherapy, such as date and location, prior to inclusion and during course of disease
- Key details on selected supportive therapies during course of disease
- Course of disease
- End of documentation – date/location/cause of death or last visit of patient
- If patients consent to cede their tumor biopsy samples to future translational research: Details on the sample (sample number, contact details of local pathology)

Table 1: Documentation schedule

<table>
<thead>
<tr>
<th>Time</th>
<th>eCRF pages</th>
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<tbody>
<tr>
<td>Inclusion</td>
<td>Registration, Demography, Tumor anamnesis incl. histology and molecular testing, Comorbidities, Prognostic factors, Prior therapies, if applicable: registration for PRO module</td>
</tr>
<tr>
<td>Throughout the project*</td>
<td>Systemic therapy (incl. outcomes), Radiotherapies and operations, Selected supportive therapies, Outcome, Course of disease</td>
</tr>
<tr>
<td>End of documentation</td>
<td>End of documentation</td>
</tr>
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</table>

* Update at least every three months.

### 6.2. Patient-reported outcomes measures (“CARe-Life”)

PRO will be assessed using the following questionnaires:


The FKSI19, version 2, is a questionnaire developed to assess the symptoms and well-being of patients with kidney cancer. It focuses on symptoms in patients during systemic therapy rated as most important by patients and clinicians (22).

#### 6.2.2. Additional items

Additional items will address common symptoms not covered with the FKSI.

### 6.3. Data source and data collection in the eCRF

All data collected in this project will be transferred from patients’ medical records to a secure web-based electronic case report form (eCRF) by the physician or trained study nurses.

iOMEDICO provides the iOstudy office EDC software for the period of the study. iOstudy office EDC is a field-tested and validated system. The eCRF is built using fully validated secure software that conforms to 21 CRF Part 11 requirements. Automatic validation programs check for data discrepancies in the eCRF and allow modification or verification of the entered data by designated study site staff.

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

After signing informed consent and before or on the first day of first systemic treatment, patients will receive and fill-in the baseline questionnaire at the study site together with a pre-paid, labelled return-envelope for mailing to iOMEDICO, where questionnaire data will be collected and analyzed.

Patient contact details (name, address) will be reported by study site personnel to the iOMEDICO Site Management Organization (iOMEDICO SMO) through a secure, web-based reporting tool. For subsequent points of time during the project, questionnaires are sent to the patient by mail by the iOMEDICO SMO. Patient contact details received by iOMEDICO SMO are strictly separated from data received and handled by iOMEDICO where the management of the project takes place and patients’ medical and questionnaire data are collected pseudonymized. Data are stored in separate databases on separate servers, and iOMEDICO SMO staff has no access to iOMEDICO databases and vice versa. The entire process has been reviewed and approved by an independent data protection registrar.

6.5. Database management and quality control

Automatic checks for plausibility and completeness of documented data are implemented in the EDC system iOstudy office 6.0. In addition, key data will be randomly and regularly checked by data managers. In case of discrepancies or missing values, study sites will be contacted. Designated site staff is required to respond promptly to enquiries and to make any necessary changes to the data. Study sites will be visited by clinical monitors to check informed consents and samples of key data.

6.6. Quality assurance site visits

Throughout the study, quality assurance monitoring will be performed by clinical monitors assigned by iOMEDICO according to iOMEDICO’s standard operating procedures (SOP). The project-specific monitoring activities are described in more detail in the monitoring plan.

By participating in the project the investigator agrees to project-related monitoring and is responsible for ensuring time and resources to provide access to source data and project-related documents to the monitor, as well as availability of the study personnel responsible for documentation at the time of the monitoring visit.

The investigator must maintain source documents for each patient in the project, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of assessments. All information recorded in the eCRF must be traceable to source documents in the patient's file.

7. Statistical methods and data analysis

Annual interim analyses will be performed. Interim reports will cover descriptive analysis of data on routine treatment including treatments applied, decision making, sequential treatments, outcome, changes over time, additional treatments, patient and tumor characteristics, molecular testing and PROs. Exploratory analyses will be performed on selected hypotheses. Questions will be specified in advance, before the respective analysis.
Categorical variables will be presented with absolute and relative frequencies, continuous variables with number of non-missing observations, and mean and standard deviation, median and 25th/75th percentiles. Time to event variables, such as progression-free and overall survival, will be analyzed using the Kaplan-Meier method. Number and frequency of events and all quartiles (25%, median, 75%) will be presented.

Regression models or matching methods can be used for exploratory analyses, if applicable. PROs will be evaluated according to the respective questionnaire manuals.

The registry analysis plan (RAP) specifies which analyses will be performed at which time point.

8. Study management and administrative procedures

8.1. Review by Ethics Committee

The project will be reviewed by the Ethics Committee of the Landesärztekammer Baden-Württemberg.

8.2. Data confidentiality

Information on study patients will be kept confidential and managed under the applicable laws and regulations.

The data collection system for this platform uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel.

8.3. Patient informed consent procedures

The investigator is responsible to fully provide patients with in-depth oral and written information about the project. If the patient understands the information and is willing to participate in the project an informed consent form will be signed. No patient data should be documented before the informed consent form has been signed. The informed consent form will be dated and signed in duplicate by both parties: the investigator that has provided the information and the patient. Each party will receive one set of the patient information and the signed consent form.

Consent for the PROs and the decentralized clinically biobank is not mandatory to participate in the project.

8.4. Withdrawal of informed consent

At any time throughout the study patients can withdraw consent without giving reasons. In case of withdrawal of consent, data documentation and further mailing of questionnaires ends and patient’s contact data are deleted. If applicable, any tumor sample provided for future translational research will not be used for further projects. Data received and documented until this point of time will remain in the study, unless the patient requests complete deletion of data. Data published prior to the withdrawal of consent will remain part of the respective publication.
8.5. Discontinuation of the study

The sponsor reserves the right to discontinue this study under the conditions specified in the study agreement.

8.6. Publication of study results

The study will be registered in a public trial registry (clinicaltrials.gov). Various publications concerning key results are planned during the course of the project.

8.7. Confidentiality of study documents and patient records

The investigator must ensure pseudonymity of the patients. Patients must not be identified by names in any documents submitted to the sponsor or entered into the eCRF. The signed patient informed consent must be kept strictly confidential at the study site.

In order to mail questionnaires to patients directly, patient identification (name and address) is reported from site personnel to iOMEDICO SMO. The patient identification is strictly separated, both in terms of database and personnel with access rights, from iOMEDICO receiving the patients’ medical and questionnaire data.

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