# Trial Description

## Title

**Randomized multi-centre open-label non-inferiority phase 3 clinical trial for patients with a stage IV childhood renal tumour comparing upfront Vincristine, Actinomycin-D and Doxorubicin (VAD, standard arm) with upfront Vincristine, Carboplatin and Etoposide (VCE, experimental arm)**

## Trial Acronym

**Randomet2017**

## URL of the trial

**[---]***

## Brief Summary in Lay Language

**The Randomet2017 study will be conducted in children and adolescents aged 3 months to 18 years who have a kidney tumor with metastasis(s). In this study, two different combinations of chemotherapeutic agents will be compared. The chemotherapy include either the drugs vincristine, actinomycin D and doxorubicin (VAD) or vincristine, carboplatin and etoposide (VCE).**
**The aim is to find out which of the two therapies is better in terms of effectiveness (probability of cure/ability to make the metastases disappear) and harmfulness (short and long-term side effects).**
**The entire study treatment includes 6 weeks of preoperative chemotherapy. Which therapy (VAD or VCE) is given is decided randomly, like a coin toss.**

## Brief Summary in Scientific Language

**Randomized multi-centre open-label non-inferiority phase 3 clinical trial for patients with a stage IV childhood renal tumour comparing upfront Vincristine, Actinomycin-D and Doxorubicin (VAD, standard arm) with upfront Vincristine, Carboplatin and Etoposide (VCE, experimental arm).**
**Additionally, importance of absolute blastemal volume and the gain of 1q for the prognosis of metastasized nephroblastoma will be investigated.**

## Do you plan to share individual participant data with other researchers?

**Yes**

## Description IPD sharing plan

**Within the framework of integrated research projects, the data will be made available to other researchers in anonymised form, insofar as this is covered by the data transfer agreement.**

## Organizational Data

- DRKS-ID: **DRKS00021160**
- Date of Registration in DRKS: **2020/05/26**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **169/19 , Ethik-Kommission bei der Ärztekammer des Saarlandes**

## Secondary IDs

- EudraCT-No.
  (for studies acc. to Drug Law): **2018-000533-13**

## Health condition or Problem studied

- Free text: **Metastatic childhood renal tumour**
- ICD10: **C64 - Malignant neoplasm of kidney, except renal pelvis**

## Interventions/Observational Groups

- Arm 1: **Preoperative chemotherapy with vincristine, actinomycin D and doxorubicin.**
  **- Actinomycin D, 1 x 45 µg/kg IV day 1 in week 1, 3, 5**
  **- Vincristine, 1 x 1,5 mg/m2 IV day 1 in week 1, 2, 3, 4, 5, 6**
  **- Doxorubicin, 1 x 50 mg/m2 6h IV-Infusion day 1 in week 1, 5**
  **Total duration: 6 weeks**
- Arm 2: **Preoperative chemotherapy with vincristine, carboplatin and etoposide.**
  **- Vincristine, 1 x 1,5 mg/m2 IV day 1 in week 1, 2, 3, 4, 5, 6**
  **- Carboplatin, 3 x 200 mg/m2 1h Infusion day 1,2,3 in week 1, 4**
  **- Etoposide, 3 x 100 mg/m2 1h Infusion day 1,2,3 in week 1, 4**
  **Total duration: 6 weeks**

## Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Active control (effective treament of control group)**

Study Type: **Interventional**

Study Type Non-Interventional: **[---]***

Allocation: **Randomized controlled trial**

Blinding: **[---]***

Who is blinded: **[---]***

Control: **Active control (effective treament of control group)**

- Purpose: **Treatment**
- Assignment: **Parallel**
- Phase: **III**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **Yes**

## Primary Outcome

**Percentage of patients with radiologic complete response (CR) of any metastasis and/or Very Good Partial Response (VGPR) of lung metastasis of childhood renal tumours after 6 weeks of preoperative chemotherapy.**

## Secondary Outcome

**Radiologic response to preoperative treatment:**
**1. Percentage of patients after 6 weeks of preoperative chemotherapy achieving a CR after surgery of metastasis at time of nephrectomy**
**2. Percentage of patients with radiologic complete response (CR) of any metastasis or Very Good Partial Response (VGPR) of lung metastasis of nephroblastoma after 6 weeks of preoperative chemotherapy**
**3. Percentage of patients with remaining metastatic disease after surgery that achieve a CR at week 9 of adjuvant chemotherapy**
**4. Percentage of patients with complete response +/- VGPR of (pulmonary) metastasis of nephroblastoma after 6 weeks of preoperative chemotherapy + 9 weeks adjuvant chemotherapy.**
**5. Percentage of patients with complete response +/- VGPR of (pulmonary) metastasis of nephroblastoma after preoperative chemotherapy + 9 weeks adjuvant chemotherapy + metastasectomy**
**6. Percentage of patients with complete response +/- VGPR of (pulmonary) metastasis of nephroblastoma at the end of adjuvant chemotherapy ± metastasectomy ± RT**
**7. Primary tumour volume shrinkage after 6 weeks of preoperative chemotherapy**
**8. Primary tumour volume after 6 weeks of preoperative chemotherapy**
**9. Number of metastases at diagnosis and after preoperative treatment**
**10. Maximum diameters of the largest metastases at diagnosis and after preoperative treatment**
**Treatment burden, complications, side effects and toxicity:**
**1. Percentage of patients requiring pulmonary radiotherapy in first line**
**2. Percentage of patients suffering from SOS during preoperative treatment according to EBMT criteria**
**3. Percentage of patients suffering any Grade 4 or grade 5 (CTCAE) toxicity during preoperative chemotherapy.**

**4. Overall duration of preoperative treatment per arm as determined as interval D1 – date of nephrectomy**
**5. Delay in timing of nephrectomy: % of patients with more than 8 weeks since start of preoperative chemotherapy because of toxicity**
**6. Percentage of (peri-)operative complications (haemorrhage, rupture, thromboembolism)**
**Outcome:**
**1. Event-free survival at 2 and 5 years for the whole cohort and according to study arm (VAD/VCE) and according to 1qGain**
**2. Overall survival at 2 and 5 years for the whole cohort and according to study arm (VAD/VCE) and according to 1qGain**

## Countries of recruitment

- BE **Belgium**
- BR **Brazil**
- DK **Denmark**
- DE **Germany**
- FR **France**
- GR **Greece**
- UK **United Kingdom**
- IE **Ireland**
- IT **Italy**
- NL **Netherlands**
- NO **Norway**
- AT **Austria**
- PL **Poland**
- PT **Portugal**
- SE **Sweden**
- CH **Switzerland**
- ES **Spain**
- CZ **Czech Republic**
- HU **Hungary**
- VA **Holy See (Vatican City State)**

## Locations of Recruitment

- University Medical Center **Homburg**
- University Medical Center **Aachen**
- University Medical Center **Augsburg**
- University Medical Center **Klinikum der LMU Dr. von Haunersches Kinderspital, München**
- University Medical Center **Berlin**
- Medical Center **Helios Berlin Buch GmbH, Berlin**
- Medical Center **Evangelisches Klinikum Bethel, Bielefeld**
- Medical Center **Klinikum Dortmund gGmbH, Dortmund**
- University Medical Center **Münster**
- University Medical Center **Bonn**
- Medical Center **Städtisches Klinikum Braunschweig gGmbH, Braunschweig**
- Medical Center **Klinikum Oldenburg AöR, Oldenburg**
- Medical Center **Gesundheit Nord Klinikum Bremen Mitte, Bremen**
- University Medical Center **Dresden**
- University Medical Center **Düsseldorf**
- Medical Center **Helios Klinikum Erfurt GmbH, Erfurt**
- University Medical Center **Erlangen**
- University Medical Center **Essen**
- University Medical Center **Frankfurt a.M.**
- University Medical Center **Freiburg im Breisgau**
- University Medical Center **Universitätsklinikum Gießen und Marburg GmbH Standort Gießen, Giessen**
- University Medical Center **Göttingen**
- University Medical Center **Greifswald**
- University Medical Center **Halle Saale**
- University Medical Center **Hamburg**
- University Medical Center **Hannover**
- University Medical Center **Heidelberg**
- University Medical Center **Jena**
- Medical Center **Klinikum Heilbronn GmbH Klinikum am Gesundbrunnen, Heilbronn**
- Medical Center **Franz Lust Klinik für Kinder - und Jugendmedizin am städtischen Klinikum, Karlsruhe**
- Medical Center **Klinikum Stuttgart - Olgahospital, Stuttgart**

- Medical Center **Gesundheit Nordhessen; Klinikum Kassel GmbH, Kassel**
- University Medical Center **Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel**
- University Medical Center **Mainz**
- University Medical Center **Köln**
- Medical Center **Kliniken der Stadt Köln gGmbH Kinderkrankenhaus, Köln**
- Medical Center **Asklepios Klinik St. Augustin, Sankt Augustin**
- University Medical Center **Leipzig**
- University Medical Center **Universitätsklinikum Schleswig-Holstein Campus Lübeck, Lübeck**
- University Medical Center **Mannheim**
- University Medical Center **Klinikum München Schwabing Kinderklinik der techn. Universität München, München**
- Medical Center **Diakonie Neuendettelsau KdöR Klinik Hallerwiese/ Cnopfsche Kinderklinik, Nürnberg**
- University Medical Center **Regensburg**
- University Medical Center **Rostock**
- University Medical Center **Tübingen**
- University Medical Center **Ulm**
- University Medical Center **Würzburg**

## Recruitment

- Planned/Actual: **Planned**
- (Anticipated or Actual) Date of First Enrollment: **2021/11/30**
- Target Sample Size: **406**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **International**

### Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **3 Months**
- Maximum Age: **18 Years**

### Additional Inclusion Criteria

**- Children <18 years at date of diagnosis and >3months**
**- Patients suffering from metastatic renal tumour at initial diagnosis, having at least one circumscript, non-calcified (pulmonary) nodule (or other lesion highly suspicious of metastasis according to criteria for metastatic disease) ≥3 mm as determined by chest CT-scan and abdominal CT-scan/MRI.**
**- Metastatic childhood renal tumour must be confirmed by central review.**
**- Signed informed consent form(s) prior to study entry according to national guidelines and GCP guidelines**
**- Voluntarily provide permission (subjects and when applicable, parental/legal representative(s)) to the ICF prior to conducting any study related assessments/procedures**
**- Able to adhere to the study visit schedule and other protocol requirements**
**- No pre-existing and ongoing cardiac malfunction disease (insufficiency, malign arrhythmias)**
**- No pre-existing and ongoing liver function deficiency that is not controllable by substitution**

### Exclusion criteria

**- Patient and/or parental/legal representative(s) denied study participation and randomization**
**- inability to be followed until two years after treatment**
**- primary nephrectomy**
**- histology other than nephroblastoma**
**- other chemotherapy prior to enrolment**
**- pregnancy or lactation**
**- Fertile female with child bearing potential and fertile male subjects who refuse using highly effective contraceptive measures**
**- Treated by any investigational agent in a clinical study within previous 4 weeks**
**- Hypersensitivity to the active substances or other excipients contained in the investigational medical products listed in the summary of product characteristics (SmPC) or Investigators Brochure (IB).**
**- any other medical condition incompatible with the protocol treatment**
**- unwillingness to follow adequate supportive measures including transfusion of**

**blood products if medically needed**
**- inability to receive chemotherapy according to the protocol, this is particulary true for:**
**a. acute kidney failure needing dialysis treatment**
**b. pre-existing peripheral neuropathy**
**- Active, uncontrolled life threatening Infection (e.g. Acute Hepatitis, Pneumonia, AIDS, Varizella)**
**- known chromosomal instability/susceptibility (e.g. Fanconi Anemia, Nijmegen Breakage Syndrome)**
**- participation in other interventional trials (registration in observational non-interventional studies is acceptable)**
**- age at start of treatment <3 months or >18 years**

## Addresses

■ **Primary Sponsor**

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## Sources of Monetary or Material Support

- **Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)**

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  URL: **[---]***

## Status

- Recruitment Status: **Recruiting planned**
- Reason, if "Recruitment stopped after recruiting started" or "Recruiting withdrawn before recruting started": **[---]***
- Reason, if Reason for Recruiting Stop "Other": **[---]***
- Study Closing (LPLV): **[---]***
- Number of Participants in Germany after Recruiting complete: **[---]***
- Total Number of Participants (all Sites worldwide) after Recruiting complete: **[---]***

## Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*