<table>
<thead>
<tr>
<th>Study title</th>
<th>Comparative Effectiveness Trial of Transoral Head and Neck Surgery followed by adjuvant Radio(chemo)therapy versus primary Radiochemotherapy for Oropharyngeal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short title</td>
<td>TopROC ; TOS vs. CRTX</td>
</tr>
<tr>
<td>Indication</td>
<td>Locally advanced, transorally resectable oropharyngeal cancer</td>
</tr>
<tr>
<td>Primary objectives</td>
<td>To evaluate the effectiveness of primary surgical versus non-surgical treatment of locally advanced, but transorally resectable oropharyngeal cancer in terms of time to local or locoregional failure or death from any cause (LRF)</td>
</tr>
</tbody>
</table>
| Secondary objectives | Effectiveness of primary surgical versus non-surgical treatment of locally advanced, but transorally resectable oropharyngeal cancer with respect to  
  - overall and disease-free survival of both treatments  
  - acute toxicity and late morbidity (including swallowing function) until 3 years after randomization  
  - Quality of life  
  - Cost-effectiveness/ cost-utility analysis |
| Tertiary objectives | Comparison of treatment effects  
  - between HPV+ and HPV- oropharynx carcinoma  
  - between different treatment modalities (surgery, radiotherapy and chemotherapy protocols) |
| Study design | Prospective, two-arm, open label, multicenter, randomized, controlled comparative effectiveness study.  
  The trial is based on an event-driven design: the final analysis will be performed when all events have been observed or the study was terminated at one of the interim analyses. |
| Study population | **Main inclusion criteria:**  
  - Histologically proven SCC of the oropharynx; T1, N2a-c, M0; T2, N1-2c, M0; T3, N0-2c, M0, with only amendable to transoral resection)  
  - Primary tumor must be resectable through transoral approach  
  - p16 immunohistochemistry by local pathology or FFPE tissue must be available for central HPV diagnostic  
  - Written and signed informed consent  
  - Briefing through surgeon and radiation oncologist  
  - ECOG PS ≤2, Karnofsky PS ≥ 60 %  
  - Age ≥ 18  
  - Curative treatment intent  
  - Adequate bone marrow function: leucocytes ≥ 3.0 x 10⁹/L, neutrophils ≥ 1.5 x 10⁹/L, platelets ≥ 80 x 10⁹/L, hemoglobin ≥ 9.5 g/dL  
  - Adequate liver function: Bilirubin ≤ 2.0 g/dL, SGOT, SGPT, ≤ 3 x ULN  
  - If of childbearing potential, willingness to use effective contraceptive method for the study duration and 2 months post-dosing.  
  - dental examination and appropriate dental therapy if needed prior to beginning of radiotherapy  
  - Nutritional evaluation prior to initiation of therapy and optional prophylactic gastrostomy (PEG) tube placement |
## Main exclusion criteria:

- Prior invasive malignancy except controlled skin cancer or carcinoma in situ of cervix
- Unknown primary (CUP), nasopharynx, hypopharynx, laryngeal or salivary gland cancer
- Metastatic disease
- Serious co-morbidity, e.g. high-grade carotid artery stenosis, congestive heart failure NYHA grade 3 and 4, liver cirrhosis CHILD C
- Hemoglobin level <9.5g/dl within 4 weeks before randomization
- Pregnancy or lactation
- Women of child-bearing potential with unclear contraception
- Previous treatment with chemotherapy, radiotherapy, EGFR-targeting agents or surgery exceeding biopsy in head and neck
- Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to study screening
- Social situations that limit compliance with study requirements or patients with an unstable condition (e.g., psychiatric disorder, a recent history of drug or alcohol abuse, interfering with study compliance, within 6 months prior to screening) or otherwise thought to be unreliable or incapable of complying with the requirements of the protocol
- Patients institutionalized by official means or court order
- Deficient dental preservation status or not accomplished wound healing

## Number of Subjects

280 patients will be randomly assigned to one of the two treatment groups.

## Study treatment

### Arm A:

- Transoral surgical resection within 4 weeks after randomization
- Neck dissection can be performed during resection of the primary tumor or within 4 weeks after randomization
- 6-7 weeks standard risk-adapted adjuvant radio-(chemo)therapy 56-66 Gy (chemotherapy according to arm B if necessary), start within 6 weeks post-surgery

### Arm B:

- 6-7 weeks standard radiotherapy (IMRT-technique), start within 4 weeks after randomization
- 70-72 Gy, SIB possible
- Cisplatin 100 mg/m² on days 1, 22, 43 or Cisplatin once weekly (30-40 mg/m²) on days 1, 8, 15, 22, 29, 36 or Mitomycin C 10 mg/m² d1, 29 and 5-FU 600 mg/m²/day iv on days 1-5 or Cisplatin 20 mg/m² + 5-FU 600 mg/m²/day iv d 1-5 and 29-33
- +/- Salvage neck dissection 12±2 weeks after treatment
<table>
<thead>
<tr>
<th><strong>Primary endpoint</strong></th>
<th>Time to local or locoregional failure (LRF) (defined as time from randomization to local or locoregional failure or death from any cause, whatever occurs first)</th>
</tr>
</thead>
</table>
| **Secondary endpoints/analyses** | • Overall and disease-free survival  
• Therapy-associated toxicity including swallowing function  
• QoL and QALY  
• Direct and indirect costs |
| **Tertiary analyses** | • Subgroup analysis of HPV+ and HPV- oropharynx carcinoma  
• Subgroup analysis of different treatment modalities (surgery, radiotherapy and chemotherapy protocols) |
| **Statistical methods** | **Sample size calculations:**  
The trial is based on an event-driven design with a planned observational period of five years (recruitment time two years and follow-up time 3 years). The event rate in the definitive chemoradiotherapy for oropharyngeal cancer group is assumed to be 50% after 36 month. The transoral head and neck surgery followed by adjuvant (chemo)radiotherapy is assumed to reduce the event rate for the primary outcome to 35%. It is assumed that the hazard rate is constant over time. Under these assumptions, 142 events have to be observed during the planned observation period, which will result in a sample size of 280 patients.  
In both arms a 3% lost to follow-up during the study is estimated. After recruiting 250 patients a blinded interim analysis will be performed. The steering committee will decide on adaptation of the sample size/ recruiting time. Additionally, based on results of the planned unblinded interim analysis after 50% and 75% of available observed events, the steering committee will decide on adaptation of the recruiting/follow up time or to allow an early stopping of the trial for success. The recruitment will be stopped immediately if the needed number of events is reached. |
| **Statistical analysis:** | The primary analysis is in the full analysis set population, consisting of all randomized patients.  
Analysis of time to event with Cox regression and Kaplan-Meier curves for both arms, adjusted to the group sequential design in a way that a two-sided overall significance level of 5% is kept. |
| **Timeline** | • Treatment period: Arm A 8-17 weeks; Arm B 6-11 weeks  
• Recruitment period: 2 years  
• Follow-up: 3 years after end of treatment of the last patient  
• Total duration of trial: approximately 64 months |
| **Study centers** | Ca. 20 centers in Germany |
Access eligibility:
Panendoscopy, FFPE, Staging, HNSCC of oropharynx

Inclusion criteria:
transoral resectable oropharyngeal cancer

Randomization 1:1

Arm A
Transoral surgical resection and neck dissection + risk-adapted adjuvant radio(chemo)therapy 56-66 Gy (+ Chemo)

Arm B
Primary Radiochemotherapy 70-72 Gy + Chemo

Prim. Endpoint: Time to local or locoregional failure
Sec. Endpoint: OS, DFS, Toxicity, QoL, QALY, cost effectiveness