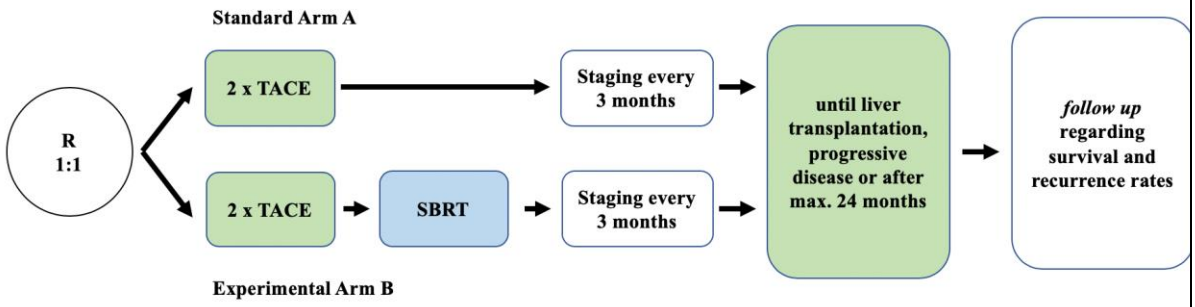
Synopsis TREASURE-TX trial

Title:

TREASURE-TX: **Tr**ansarterial chemo**e**mbolization (TACE) **a**nd **s**tereotactic body radiation (SBRT) in patients with hepatocell**u**lar ca**r**cinoma (HCC) prior to liv**e**r transplantation

Trial design:

This is a randomized, multicenter phase II study with two arms. Patients suffering from **early HCC (BCLC A) and planned for liver transplantation** are randomized in a 1:1 ratio to investigate the efficacy, quality of life, and safety of **TACE alone versus the combination of TACE and SBRT** as bridging therapy to liver transplantation. Two procedures of TACE are performed with no further SBRT (Arm A) or with following SBRT (Arm B). Primary endpoint is progression free survival, secondary endpoints histopathology after liver transplantation. Patients are followed up with regard to survival and recurrence rates for two years after first TACE procedure.



Sponsor:

AIO Studien gGmbH

Number of patients:

2 x 22 patients

Number of trial sites:

up to 20 trial sites

Clinical Phase:

Phase II

Indication studied:

Early HCC

Study Duration:

First patient in to last patient out:

Enrollment: 36 months

Treatment: 2 TACE procedures with an interval of four weeks each (q4w +/- 1wk), followed by SBRT. Additional therapies allowed upon progression.

Study duration/observation period: 24 months after last treatment or until liver transplantation Follow up: 2 months after observation period
Investigational and Reference Therapy: **Arm A (control):** The patients will receive two or more procedures of TACE as clinically indicated prior to liver transplantation. **Arm B (experimental):** The patients will receive two procedures of TACE followed by SBRT prior to liver transplantation. Additional treatment of lesions is possible upon progression (investigators choice).
Background and rationale: In patients with tumors within Milan criteria, liver transplantation remains a curative therapeutic option even if liver resection is not feasible. Due to organ shortage, there are long waiting periods and waitlist withdrawal because of tumor progression remains an eminent risk[1]. Hence bridging therapies are used to halt tumor growth. Transarterial chemoembolization (TACE) is one of the most common used bridging therapies.[2,3]. Other possible bridging therapies are local ablation[4] and stereotactic body radiation therapy (SBRT)[5,6]. Importantly, there are several studies showing a potential benefit of the combination of TACE and SBRT in the treatment of HCC[7-9]. Recently we were able to show a high rate of complete histopathological response in patients who were treated with a combination of TACE and SBRT as bridging to liver transplant, suggesting a potential benefit in combining both therapies in the pre-transplant setting[10].
Safety considerations: Though TACE is low in side effects, it can lead to a deterioration of liver function in some patients[11]. To minimize the possible risks, only two TACE procedures are planned to be performed as study treatment. SBRT shows a good safety profile in patients with HCC[12]. Furthermore, only patients with preserved liver function and small tumor nodules up to maximum 5 cm are included into the study.
Research Hypothesis: A combination of TACE and SBRT in patients with HCC waiting for liver transplantation leads to improved tumor control in comparison to TACE alone.
Study Design: Phase II, randomized, prospective, multicenter, 2-armed, open-label
Objectives: **Primary Endpoint:** Progression free survival (PFS) **Secondary Endpoints:** radiological response rate (overall response rate (ORR), complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD)) determined by modified response evaluation criteria in solid tumors (mRECIST), histopathological response (presence of vital tumor tissue) in explant histopathology after liver transplantation as well as percent of vital tumor tissue in explant livers, overall survival (OS), changes in quality of life (QoL)

from baseline to study end/end of treatment, adverse events (AEs) and severe adverse events (SAEs), recurrence rate after liver transplantation **Exploratory Objectives:** Effect of maximal tumor size, number of lesions, albumin-bilirubin score (ALBI Score), Child Pugh Score, alpha-fetoprotein (AFP).
Translational research: Correlation of objective response according to mRECIST and correlation of OS/PFS with immune-related biomarkers in serum (i.e. AFP, CRP). Analysis of PBMCs for immunological predictors of tumor response. Presence of cell free tumor DNA in patient blood samples.
Study Population: Patients diagnosed with early HCC (BCLC A) planned for liver transplantation and without prior tumor specific therapy within the last two years.
Statistical methods and sample size: Two study arms, each with a significance level of 0.025, power of 80%. Resulting in a sample size of 22 patients per group. In total n = 44 patients.
Key Inclusion criteria: 1. Early-stage HCC (BCLC A), diagnosed according to EASL or AASLD criteria, without any curative treatment option (resection or ablation) except for liver transplantation as determined by tumor board decision. 2. Patients planned for liver transplantation after discussion within a multidisciplinary board. Patients do not need to on the wait list for liver transplantation for randomization and treatment. 3. Patients eligible to receive SE-MELD Score according to German transplant regulations. 4. At least one measurable site of disease with spiral CT scan or MRI.
Key Exclusion criteria: 1. Prior local tumor specific treatment of the same tumor nodule within the last 24 months. 2. Preexisting liver cirrhosis according to Child-Pugh Class B > 8. 3. Presence of tumor lesions not amenable to TACE or SBRT as determine by central review board. 4. Prior radiotherapy to the upper abdomen
Treatment, dosage and administration: TACE is performed as clinical standard followed by SBRT in the experimental arm as described below: **Arm A (Standard Arm):** Two procedures of TACE will be performed for all viable tumor lesions within a time interval of four weeks (possible range of three to five weeks). TACE will be performed according to Medical

Guidelines with licensed, CE marked medical devices according to the local standard of care in each trial center. TACE will be performed as selectively as possible. Additional tumor therapy will be allowed upon progression or incomplete response after discussion within a multidisciplinary board.

Arm B (Experimental arm):

Two procedures of TACE will be performed for all viable tumor lesions within a time interval of four weeks (possible range of three to five weeks). TACE will be performed according to Medical Guidelines with licensed, CE marked medical devices according to the local standard of care in each trial center. TACE will be performed as selectively as possible.

SBRT will be initiated within 7-14 days from second TACE, unless significant medical events have not resolved. SBRT will be performed according to Medical Guidelines with licensed, Conformité Européene (CE) marked medical devices according to the local standard of care in each trial center.

Safety:

A safety interim analysis will be conducted as additional safety monitoring, once the first 5 patients in each arm have completed two procedures of TACE and SBRT. The results of this safety interim analysis will be presented to an independent Data Safety Monitoring Committee, that will give recommendations on how to proceed with the study. This Data Safety Monitoring Committee will also evaluate safety data during the study on a periodic basis. In addition to the planned safety review, additional unscheduled meetings may take place at request of a Data Safety Monitoring Committee member or the sponsor.

GCP statement:

The clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the applicable regulatory requirements.

References

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