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TRANSMIT: Utilizing discarded livers from donors with a history of cancer for patients lacking access to standard allocation - A compassionate use exploratory study☆

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ABSTRACT

Background: A substantial number of viable donor livers are discarded due to the donor's underlying malignancy. Concurrently, patients with certain liver malignancies – such as unresectable colorectal cancer liver metastases (CRC-LM), unresectable intrahepatic or perihilar cholangiocarcinoma (iCCC/phCCC), or unresectable hepatocellular carcinoma (HCC) responding to immunotherapy – often face poor survival outcomes and are deemed ineligible for potentially curative liver transplantation. In this context, a rational risk-benefit analysis suggests that transplanting an organ with a theoretical risk of tumor transmission may be justifiable for these patients facing otherwise short-term fatal outcomes.

Methods: The TRANSMIT study is a compassionate use exploratory study aimed at assessing the utility and safety of using donor organs from individuals with a current or past history of cancer for liver transplantation in patients with liver malignancies (CRC-LM, i/phCCC, HCC) who are not eligible for regular organ allocation. The study will evaluate the utilization rate of donor organs that would otherwise be discarded, overall survival, progression-free survival, and tumor transmission rates at one and three years, stratified by indication.

Discussion: Donor organs from individuals with a current or past history of cancer may represent a valuable and safe resource for expanding the limited donor pool, particularly for patients who lack access to standard organ allocation.

1. Introduction

1.1. Background and Rationale (6)

Liver transplantation (LT) remains one of the most effective treatments for end-stage liver disease and certain unresectable liver malignancies. However, the persistent and severe shortage of donor organs significantly limits access to life-saving liver transplants. As a result, thousands of patients die each year, either while waiting for a suitable donor or because they are not eligible for liver transplantation. The growing disparity between supply and demand has prompted researchers and transplant centers to explore unconventional avenues to expand the donor pool. One such approach is the consideration of livers from donors with a current or past history of cancer, a donor category that has traditionally been excluded due to concerns about tumor transmission.

☆ Further functional carriers and organizational structures are co-investigators, monitor, biostatistician, steering committee, and data monitoring committee (DMC).

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[1] Name and contact information for the principal investigator: Professor Markus Guba; Department of General, Visceral and Transplant Surgery, LMU University Hospital Munich, LMU Munich, Germany; markus.guba@med.uni-muenchen.de.Role of principal investigator: The principal investigator (PI) is responsible for the administration of the study and collection and interpretation of data. The PI will also take a leading part in writing reports and submitting publications. Decisions will be taken in collaboration with all investigators in the study.

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Historically, active malignancy or a history of certain cancers has been viewed as a contraindication for organ donation due to the theoretical risk of transmitting cancer cells to the recipient. However, recent advancements in cancer diagnosis, treatment, and surveillance have prompted a re-evaluation of this risk. Organs from donors with primary brain tumors, for example, are widely accepted, given the low likelihood of systemic metastasis [1]. Similarly, organs from individuals with treated and cured malignancies, where the risk of recurrence is minimal, have also been used in some cases with encouraging outcomes. These examples suggest that, in select circumstances, donor livers from individuals with a current or past history of cancer may be a viable option for transplantation.

Small sample sizes, retrospective analyses, and inconsistent reporting across transplant centers limit current data on the safety of using organs from cancer-affected donors [2,3]. As a result, the true risk of tumor transmission remains uncertain. Tumor transmission, while rare, can lead to significant morbidity and mortality in recipients [4]. However, the risk must be balanced against the potentially life-saving benefits of transplanting a liver into a recipient who may otherwise die from liver failure or unresectable malignancy. Emerging evidence suggests that the risk of tumor transmission may be acceptable in specific donor-recipient scenarios, particularly when donors have a history of localized cancers with low metastatic potential or have been in remission for a significant period of time.

The potential benefit of utilizing livers from cancer-affected donors is particularly pronounced in patients with advanced liver disease or unresectable liver malignancies who have exhausted other treatment options. For these patients who face short-term mortality without transplantation, the use of a liver with a theoretically higher risk of tumor transmission may represent a justifiable and life-saving option. Given the dire prognosis of such recipients, the possibility of cancer recurrence or transmission may be outweighed by the immediate survival benefit offered by the transplant.

The TRANSMIT study focuses on three key indications - colorectal cancer liver metastases (CRC-LM), intrahepatic and perihilar cholangiocarcinoma (iCCC/phCCC), and advanced hepatocellular carcinoma responding to immunotherapy (HCC) - which have historically been excluded from standard allocation due to concerns over high recurrence rates and poor post-transplant outcomes. However, recent advancements in systemic therapies, particularly immunotherapy, have challenged this conventional perspective, opening new possibilities for LT as a viable option for patients with these previously contraindicated liver malignancies.

1.1.1. Colorectal Cancer Liver Metastases (CRC-LM)

The pioneering Norwegian SECA studies have shown that selected patients can achieve 5-year survival rates exceeding 50 % post-transplantation, comparable to outcomes in other benign liver diseases [5]. More recently, the TransMet trial demonstrated that LT combined with systemic therapy significantly improved 5-year overall survival (OS) compared to systemic therapy alone, with rates of 73 % versus 9 %, respectively. However, despite this marked survival benefit of LT combined with systemic therapy, the trial reported relatively low 5-year progression-free survival (PFS), with rates of 20 % compared to 0 % for systemic therapy alone [6]. The Toronto group significantly improved outcomes by applying more rigorous selection criteria, achieving a 3-year OS rate of 100 % and a 3-year disease-free survival (DFS) rate of 68.6 % [7].

1.1.2. Intrahepatic/perihilar Cholangiocarcinoma (iCCC/phCCC)

1.1.2.1. iCCC. In patients with early-stage intrahepatic cholangiocarcinoma (iCCC), liver resection is the primary curative treatment option. However, there is a subset of patients with iCCC who are not eligible for resection due to impaired liver function, often caused by underlying cirrhosis or for technical reasons. Although initial outcomes were poor, recent studies have shown improved survival rates due to better selection criteria and the use of neoadjuvant therapy. Sapisochin et al. reported that patients with "very early" iCCC (single tumor $\leq$2 cm) and cirrhosis had a 5-year OS rate of 65 %, suggesting that these patients could be considered candidates for LT [8]. Further pooled analyses of iCCC patients who underwent LT demonstrated a 5-year OS rate of 71 % in patients with very early iCCC, comparable to the currently accepted threshold of 75 % for HCC [9]. Several other studies have also indicated that long-term survival following LT in iCCC patients, particularly those with early-stage disease, may be comparable to that following resection [10–12]. The risk of recurrence after LT increases with larger tumor size, microvascular invasion, and elevated CA 19-9 levels.

1.1.2.2. phCCC. LT is considered a viable option for patients with locally advanced but non-metastatic perihilar cholangiocarcinoma (phCCC), where achieving an R0 resection is technically infeasible. The introduction of combined preoperative chemoradiotherapy by the Mayo Clinic group significantly reduced the previously high recurrence rates, which had ranged from 53 % to 84 %. Despite criticism of this study due to its small sample size and cases where no tumor was detected in the final explant, it reported a 5-year survival rate of 82 %. Based on the Mayo protocol, several additional studies have been conducted. A multicenter evaluation of 304 patients who underwent either liver resection or LT demonstrated superior 5-year survival rates of 64 % in the LT group, compared to 18 % for resection alone. In a subgroup analysis, the authors concluded that even for nodal-negative tumors smaller than 3 cm, LT outperformed resection [13].

A 2021 meta-analysis by Cambridge et al. included 428 patients from 20 studies and reported pooled 1-, 3-, and 5-year OS rates of 71 %, 48 %, and 32 %, respectively. The use of neoadjuvant therapy significantly improved 1-, 3-, and 5-year OS to 83 %, 66 %, and 65 %, respectively. The recurrence rate was 24 % at three years when neoadjuvant therapy was employed, compared to 52 % without its use [14]. The value of neoadjuvant therapy has been repeatedly emphasized in other studies. For instance, Rea et al. found that 42 % of explanted livers showed no residual tumor [15]. Similarly, Ethun et al. reported lower rates of perineural invasion (33 % vs. 78 %) and lymph node positivity (19 % vs. 38 %) following chemoradiotherapy compared to resection alone. In Germany, patients who successfully complete the protocol can apply for MELD exception points for unresectable phCCC to prioritize their candidacy for LT.

1.1.3. Advanced Hepatocellular Carcinoma (HCC) Responding to Immunotherapy

For a subset of HCC patients who achieve significant tumor regression or disease control under immunotherapy, liver transplantation may offer the potential for long-term survival. Preliminary evidence suggests that in patients with advanced HCC who respond to immunotherapy, post-transplant outcomes can approach those of patients with early-stage disease if the transplant is performed after achieving sustained disease control. In a U.S. VITALITY registry study of 117 HCC patients who were downstaged to within Milan Criteria (MC) after receiving immunotherapy, the 1- and 3-year intention-to-treat (ITT) survival rate was 94.6 % and 70.8 %, and 92.1 % and 85 % among those who underwent transplantation. Radiographic partial (HR 0.21) or complete (HR 0.16) responses were the strongest predictors of improved ITT survival, while non-response or disease progression was associated with poorer outcomes [16]. Most of the evidence on LT following immunotherapy has been derived from case series recently analyzed in a meta-analysis by Rezaee-Zavareh. The analysis reported a 5-year OS rate of 88 % for patients without rejection and 83 % for those experiencing rejection [17]. Rejection rates were generally higher with shorter immunotherapy washout periods, with rejection risk normalizing around three months post-treatment.

1.2. Objectives (7)

The TRANSMIT study represents a novel and pragmatic response to the double challenges of organ scarcity and the exclusion of high-risk cancer patients from transplant eligibility. By expanding the donor pool to include organs from individuals with a current or past history of cancer and offering these organs to patients who would otherwise be excluded from transplantation, the study aims to provide potentially curative liver transplantation for a population that has no alternative treatment options and been historically underserved by current organ allocation practices. With this approach, the study evaluates the utility, safety, and outcome of transplanting donor livers from patients with a current or past history of cancer.

1.3. Trial Design (8)

TRANSMIT is a compassionate use, exploratory study.

2. Methods: Participants, Interventions, and Outcomes

2.1. Study Setting (9)

The study will be conducted at the Department of General, Visceral, and Transplant Surgery, LMU University Hospital, LMU Munich, Germany. This study is planned as a single-center study but is, in principle, accessible to all Eurotransplant centers upon request.

2.2. Eligibility Criteria (10)

2.2.1. General Inclusion Criteria

- Age between 18 and 65 years.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0–1.
- Full eligibility and fitness to undergo liver transplantation.
- Full eligibility and fitness to receive effective neoadjuvant or adjuvant systemic therapy.
- Presence of non-resectable disease.
- Absence of extrahepatic disease.
- Approval from the interdisciplinary national tumor board.
- Approval from the interdisciplinary liver transplant board.

2.2.2. Tumor-specific Inclusion Criteria

2.2.2.1. Colorectal Cancer Liver Metastases (CRC-LM).

- Primary tumor resected at least 6 months prior.
- Primary tumor stage of T4a or lower, with R0 resection (complete tumor removal).
- Absence of BRAF V600 mutation due to the expected poor outcome in metastatic colorectal cancer [18].
- Absence of microsatellite instability-high (MSI-H)/deficient mismatch repair (dMMR) status due to expected excellent response to checkpoint inhibitors/immunotherapy [19–23]. Exception: MSI-H/dMMR with poor response to checkpoint inhibitors/immunotherapy but no disease progression for at least 6 months to subsequent therapies.
- No disease progression for at least 6 months, confirmed by MRI, CT, or FDG-PET/CT imaging within 4 weeks prior to inclusion.
- Carcinoembryonic antigen (CEA) level $\leq$100 ng/ml at the time of the last pre-transplant evaluation.

2.2.2.2. Intrahepatic/Perihilar Cholangiocarcinoma (iCCC/phCCC).

- Functionally unresectable single tumors $\leq$3 cm in a cirrhotic liver or technically unresectable single tumors $\leq$5 cm in a non-cirrhotic liver.
- No disease progression under systemic therapy, immunotherapy, or local ablative therapy for at least 3 months, confirmed by MRI, CT, or FDG-PET/CT imaging within 4 weeks prior to inclusion.
- CA19-9 level $\leq$100 ng/ml at the time of the last pre-transplant evaluation.
- FDG-PET/CT negative for nodal or distant metastasis at the time of the last pre-transplant evaluation.

2.2.2.3. Hepatocellular Carcinoma (HCC).

- Diagnosis of HCC that initially exceeded standard allocation criteria.
- No disease progression under systemic therapy, immunotherapy, or local ablative therapy for a minimum of 6 months, confirmed by MRI, CT, or FDG-PET/CT imaging within 4 weeks prior to inclusion (with at least 42 days elapsed since the last immunotherapy treatment).
- Alpha-fetoprotein (AFP) level $\leq$20 ng/ml at the time of the last pre-transplant evaluation.

2.2.3. Eligible Donors

- ABO-compatible donors with a current or past history of cancer who have been declined after being offered through all other Eurotransplant allocation regimens (patient-directed, center-directed, and rescue allocation) may be considered for acceptance.
- The organ is not suitable for any other patient on the regular waiting list.
- Apart from the donor's current or past history of cancer, no other significant marginality criteria that would elevate the risk of primary graft non-function, necessitating re-transplantation.
- The anticipated risk of tumor transmission must be considered acceptable in an individualized risk-benefit assessment (ranging from minimal risk (<0.1 %), low risk (0.1–2%), intermediate risk (2–10 %) to high risk (>10 %)), in accordance with the 2022 guidelines on the quality and safety of organs for transplantation, as recommended by the European Directorate for the Quality of Medicines & HealthCare (Council of Europe) [24].

2.3. Interventions (11)

2.3.1. Liver Transplantation and Best-Established Treatment

Patients awaiting LT will receive individualized oncological therapy during the waiting period, with the dual objectives of maintaining disease stability while minimizing adverse effects that could compromise eligibility for transplantation.

The target is to perform the LT within 12 weeks of the patient's placement on the waiting list. However, due to organ shortages, waiting times may extend beyond this window. There is no upper time limit on the waiting list, provided the patient continues to meet the study criteria. The surgical procedure will be conducted following standard LT protocols.

Careful attention is given to existing imaging of the organ donor to identify any liver lesions that may suggest liver involvement from a pre-

existing malignancy. Prior to transplantation, an additional ultrasound examination of the donor liver is conducted during hypo- or normothermic oxygenated machine perfusion to rule out any clinically detectable liver lesions.

Following transplantation, patients may resume adjuvant oncological therapy tailored to the post-transplant clinical context at the discretion of the oncology team.

2.3.2. Immunosuppressive Management

Following LT, patients are administered a standard triple immunosuppressive regimen consisting of low-dose tacrolimus (TAC [or equivalent]; C_0 5–8 ng/ml), mycophenolate mofetil (MMF [or equivalent]; 500 mg twice daily), and steroids. Steroids are tapered and discontinued no later than three months post-transplant. After six weeks, MMF should be replaced with Everolimus (EVE, C_0 3–6 ng/ml), an mTOR inhibitor known for its anti-tumor properties [25,26]. By this time, TAC should be adjusted to maintain a target trough level of 2–5 ng/mL. The combined trough levels of TAC and EVE should total approximately 8–10 ng/mL.

Additionally, patients will receive standard anti-infective prophylaxis for six months, including sulfamethoxazole-trimethoprim and valganciclovir.

2.4. Outcomes (12)

The primary objective of this study is to assess the utilization rate of donor organs that would otherwise be discarded (utilization rate = total number of organs used/total number of organs offered; offered via second-line rescue allocation, previously declined for donor malignancy, otherwise no other marginality criteria that would preclude successful transplantation).

Secondary objectives include evaluating OS at one and three years, stratified by indication, as well as determining PFS at one and three years, with recurrence described separately as hepatic and extrahepatic.

Additionally, the tumor transmission rate at one and three years will be monitored to ensure the safety of using donor grafts from individuals with a current or past history of cancer. Therefore, types of cancer after liver transplantation are classified as:

- Donor transmitted cancer (DTC), which is present within the allograft at the time of transplantation [27].
- Donor derived cancer (DDC), which develops within the donor cells following transplantation [27].
- De novo cancer, which develops from the recipient cells as a long-term consequence of transplantation [27].
- Recurrent cancer, which is the recurrence after transplantation of cancer that the recipient had treatment for, before transplantation [27].

DTC is relevant for the calculation of the tumor transmission rate. DDC, de novo cancer, and recurrent cancer have to be excluded.

Since tumor transmission and other underestimated long-term risks may manifest beyond the three-year follow-up, regular post-study surveillance in our liver transplant outpatient clinic is planned.

2.5. Participant Timeline (13)

The participant timeline is shown in Fig. 1.

2.6. Sample Size (14)

Given that this is an all-or-nothing compassionate use setup, a formal sample size calculation is not feasible. However, based on a hypothetical effect size of 100 % versus 0 %, with an alpha of 0.05 and a power of 90 %, the estimated sample size for the primary endpoint is 10 patients. To collect meaningful data on secondary endpoints, we aim to include 20 patients, targeting one patient every three months, or more over a 60-month recruitment period. If additional centers within the Eurotransplant region participate, we aim to recruit a total of 60 patients, with one patient per month. Regarding the unlikely event of low recruitment within 60 months, an additional 12 months of recruitment will be added.

2.7. Recruitment (15)

Information about the study and the opportunity for patient enrollment has been communicated to attending oncologists, as well as colorectal and hepatopancreatobiliary (HPB) surgeons. The Standing Commission on Organ Transplantation of the German Medical Association, the German Organ Transplantation Foundation (DSO), and relevant bodies of Eurotransplant have been notified of the study. The study was announced to be open for other Eurotranplant liver transplant programs. The anticipated enrollment period is expected to span 60 months.

(16 and 17) not applicable.

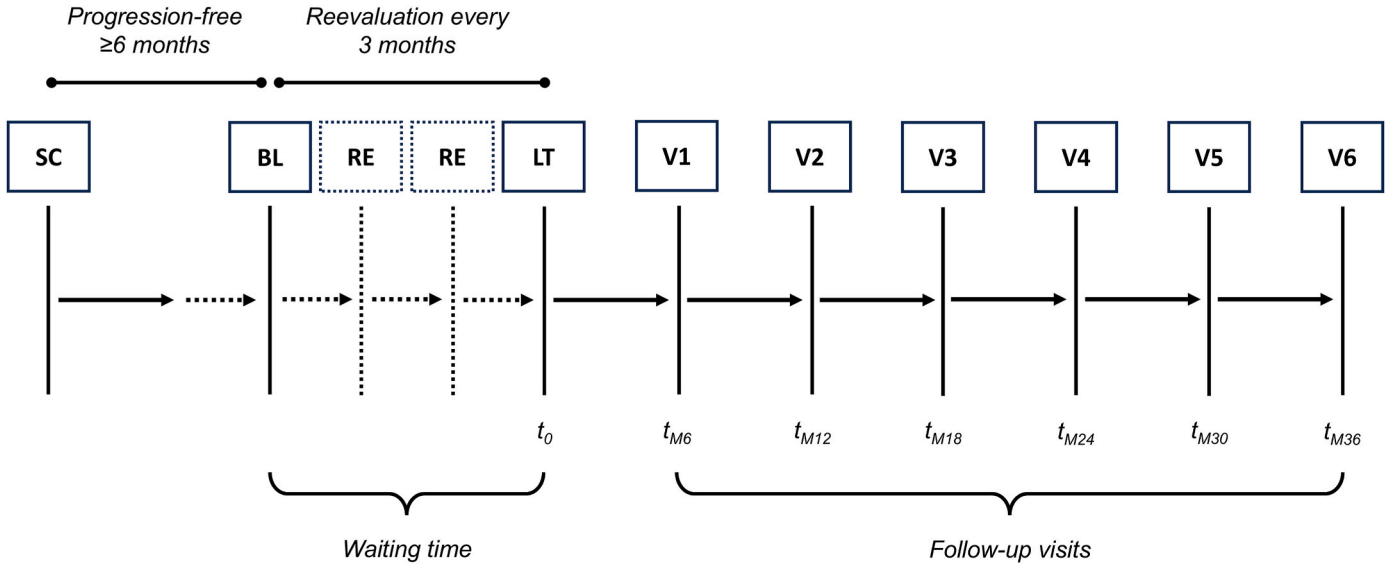

Fig. 1. Schedule of enrolment, intervention, and assessment (according to SPIRIT); SC, screening; BL, baseline; RE, reevaluation; LT, liver transplantation; V, follow-up visits.

3. Methods: Data Collection, Management, and Analysis

3.1. Data Collection Methods (18)

3.1.1. Plans for Assessment and Collection of Outcome, Baseline, and Other Trial Data (18a)

Patients will be monitored for a duration of three years. Study visits will occur at baseline (BL) and every six months for the first three years after LT (see Fig. 1). Follow-up evaluations will include mandatory diagnostic imaging (MRI or CT of the liver and CT of the thorax), blood tests including tumor markers, and plasma sample collection for liquid biopsy analysis.

3.1.2. Plans to Promote Participant Retention and Complete Follow-up (18b)

All study participants, except those who withdraw consent, will be followed throughout the study period. Patients who discontinue follow-up visits without formally withdrawing consent will continue to be monitored for survival outcomes.

3.2. Data Management (19)

The designated site staff will enter protocol-required data into REDCap-based electronic case report forms (eCRFs). The principal investigator is responsible for ensuring that the data entered into the eCRFs is complete, accurate, and entered in a timely manner. The study site co-investigator will confirm the accuracy and completeness of the data.

3.3. Statistical Methods (20)

TRANSMIT is a compassionate use, exploratory study.

The patients will be continuously monitored by the medical staff, primarily from the transplant outpatient clinic and oncology team at the respective study site. As a result, the likelihood of missing follow-up appointments is expected to be low.

For the primary outcome, which is the utilization rate of donor organs that would otherwise be discarded, the amount of missing data is anticipated to be minimal. For parameters with a higher rate of missing outcomes, the characteristics of participants without observed outcomes and the reasons for the missing data will be reported.

4. Methods: Monitoring

4.1. Data Monitoring (21)

A data monitoring committee (DMC) is appointed consisting of clinicians and a biostatistician who are independent of the trial. The DMC will perform the interim analysis where they will analyze the safety of the trial.

Interim analysis will be conducted after one year. The PI has the right to terminate or change the trial prematurely if there are any medical or ethical concerns. Premature termination of the trial will be considered if there are safety reasons – i.e. unexpected high transmission rates above 10 % – or if new publications clearly show that other therapy options are more beneficial for patients that fulfill TRANSMIT inclusion criteria.

In case of a prematurely stopped trial, the patients will be taken care of and followed at the discretion of the treating physician.

4.2. Harms (22)

Tumor transmission will be reported as a serious adverse event (SAE). All other potential SAEs and adverse events (AEs), that fall within the expected scope of liver transplantation will be recorded to achieve a comprehensive evaluation of postoperative outcomes. This includes the assessment of postoperative graft function, graft rejection, recurring patient listing, and high-urgency listing.

4.3. Auditing (23)

The PI is responsible for supervising the clinical study to ensure the protection of participants' human rights, safety, and well-being, as well as ensuring that the study is conducted according to the current protocol. Additionally, the PI ensures that the data reported by co-investigators are accurate, complete, and verifiable against study-related records, including source documents. An independent study monitor (member of the "Koordinationszentrum Chirurgische Studien (KCS)", Department of General, Visceral and Transplant Surgery, LMU University Hospital, LMU Munich, Germany) has been appointed by the PI for proper oversight.

5. Ethics and Dissemination

5.1. Research Ethics Approval (24)

The TRANSMIT study was approved by the Ethics Committee of the LMU Munich and is registered with the number 23–0921.

5.2. Protocol Amendments (25)

Any modifications to the study that occur after protocol approval will be recorded as either protocol amendments or administrative amendments. Depending on the nature of the amendment or revision, approval or notification from the Ethics Committee may be required. Changes will only be implemented after obtaining approval from both the PI and the Ethics Committee, if applicable. Written confirmation of the Ethical Review Agency's approval will be secured before any amendment is put into effect.

5.3. Consent or Assent (26)

The study nurse or treating surgeon will be obtaining informed consent from potential trial participants. Additional consent provisions for the collection and use of participant data and biological specimens are obtained by our pre-existing biobank at the LMU University Hospital Munich.

5.4. Confidentiality (27)

All patient data collected and processed for the purposes of this study will be handled by the PI with appropriate safeguards to ensure confidentiality, in compliance with national laws and regulations on personal data protection. The study will adhere to the General Data Protection Regulation (GDPR) to protect sensitive personal information and will be conducted in accordance with the World Health Organization (WHO) guidelines for Good Clinical Practice (GCP).

5.5. Declaration of Competing Interests (28)

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

5.6. Access to Data (29)

The TRANSMIT steering committee, including the trial biostatistician, has full access to the trial data. Any data required to support the protocol can be supplied on request.

5.7. Ancillary and Post-trial Care (30)

No provision for post-trial care will be offered.

5.8. Dissemination Policy (31)

Upon study completion and finalization of the study report, the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results. The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations. All personnel who have contributed significantly to the planning and performance of the study (Vancouver Convention 1988) may be included in the list of authors.

The protocol is available to the public, but the dataset and statistical codes will not be made publicly available to protect the confidentiality of the participants.

6. Appendices

6.1. Informed Consent Materials (32)

A standardized consent form for the TRANSMIT study is given to participants and authorized surrogates. For collection and use of participant data and biological specimens, a pre-existing consent form of or biobank at the LMU University Hospital Munich is used. In addition, all consent forms that are usual for a standard liver transplantation will be obtained.

6.2. Biological Specimens (33)

Plasma samples will be collected at baseline and each study-related visit throughout the study period. Tissue samples from the primary liver tumor or metastases, along with macroscopically normal liver tissue, will also be collected. Following preparation and aliquoting, both plasma and tissue samples will be stored at −80 °C in a pre-existing biobank at the LMU University Hospital Munich or temporarily at respective study sites.

7. Discussion

One of the central concerns in the TRANSMIT study is the potential risk of tumor transmission from donors with a current or past history of cancer to the recipient. Tumor transmission is a known, albeit rare, complication of organ transplantation, and the use of organs from donors with a malignancy history elevates this risk. While organs from donors with certain cancers, such as primary brain tumors, have traditionally been deemed safe due to the low risk of metastasis beyond the central nervous system, the same cannot be stated for other cancer types. This necessitates a cautious approach to donor selection and a thorough assessment of potential risks.

In the context of the TRANSMIT study, the risk of tumor transmission must be weighed against the immediate survival benefit offered to patients with unresectable liver malignancies. These patients face an otherwise grim prognosis without transplantation, making the potential benefit of receiving a liver from a donor with a history of cancer particularly high. However, the possibility of tumor transmission, even if small, could result in significant post-transplant complications, including metastatic disease, which would severely impact both survival and quality of life.

To mitigate this risk, the study incorporates stringent donor selection criteria. Only donors with an anticipated risk of tumor transmission considered to be acceptable in an individualized risk-benefit assessment (ranging from minimal risk to high risk), as outlined by the 2022 European guidelines for the quality and safety of organs for transplantation, are considered [24]. In addition to available donor imaging, a preoperative ultrasound assessment of the donor liver is conducted to identify any clinically significant liver lesions that may indicate cancerous involvement. Despite these precautions, a degree of uncertainty remains, as some microscopic or undetectable metastases could still be transmitted to the recipient.

Another factor influencing the risk of tumor transmission is the recipient's immunosuppressive regimen post-transplant. Immunosuppression is necessary to prevent graft rejection, but it also creates a permissive environment for cancer cells to proliferate. The study's protocol includes the use of mTOR inhibitors like Everolimus, which have demonstrated anti-tumor properties, in an effort to reduce the likelihood of tumor recurrence or transmission in the post-transplant setting [25,26]. However, the balance between effective immunosuppression and cancer control remains delicate and requires careful monitoring. Long-term follow-up is essential to fully understand the risk of tumor transmission. The study monitors transmission rates at both one and three years post-transplant, but it is possible that some cases of tumor transmission may manifest later, potentially underestimating the true long-term risk.

The TRANSMIT study is designed as a compassionate use, exploratory trial aimed at assessing the feasibility and safety of utilizing discarded donor livers from individuals with a history of cancer. The study's design is structured to address the critical shortage of organs for transplantation, specifically targeting patients with unresectable liver malignancies who are not eligible for standard organ allocation. By offering these patients organs that would otherwise be discarded, the study explores a novel approach to expanding the donor pool, with a focus on maximizing survival for a high-risk population.

One of the key strengths of the study design is its inclusion of rigorous donor and recipient selection criteria. On the donor side, organs are carefully vetted to ensure that the risk of tumor transmission is acceptable in an individualized risk-benefit assessment based on established European guidelines. This cautious approach is crucial for minimizing the risk to recipients while exploring the boundaries of using organs from cancer-affected donors. For recipients, the inclusion criteria prioritize patients with controlled disease, favorable tumor biology, and good performance status, thereby selecting those with the highest potential for a positive outcome post-transplantation.

The study's primary endpoint - the utilization of previously discarded organs - addresses the core objective of the research: increasing the availability of organs for patients who would otherwise have no options. This endpoint provides a practical measure of the success of the intervention in expanding the donor pool and directly correlates with the study's broader aim of addressing organ scarcity. Secondary endpoints, including overall survival (OS), progression-free survival (PFS), and tumor transmission rates, are appropriate for assessing both the efficacy and safety of the transplant procedure. Stratifying these outcomes by specific malignancies (CRC-LM, iCCC/phCCC, and HCC) allows for a more nuanced understanding of how different tumor types respond to this approach. The study also monitors tumor transmission at one and three years, providing valuable insights into both short- and medium-term risks associated with these transplants.

However, the study design faces several challenges. One potential limitation is the relatively small and highly selected patient population, which may reduce the generalizability of the findings to a broader group of liver transplant candidates. The strict inclusion criteria, while necessary for minimizing risk, may limit the applicability of the results beyond the specific population chosen for the study. Additionally, the small sample size may reduce the statistical power to detect rare events, such as tumor transmission, or subtle differences in survival outcomes. Another potential challenge is the logistical complexity of organ allocation in this context. The study relies on organs that have been declined through multiple Eurotransplant allocation pathways, meaning that the timing and availability of organs may be unpredictable. This could result in extended waiting periods for recipients, potentially impacting the study's ability to meet enrollment and transplantation targets within the proposed time frame.

In conclusion, the TRANSMIT study's design is innovative and well-suited to addressing the pressing issue of organ scarcity for liver transplant patients with unresectable malignancies. The study's rigorous

selection criteria and careful monitoring of outcomes offer a strong framework for evaluating the feasibility and safety of using organs from cancer-affected donors.

CRediT authorship contribution statement

Dominik Thomas Koch: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Malte Schirren:** Writing – review & editing, Validation. **Severin Jacobi:** Writing – review & editing, Validation. **Christian Lange:** Writing – review & editing, Validation. **Jens Werner:** Writing – review & editing, Supervision. **Dionysios Koliogiannis:** Writing – review & editing, Validation. **Markus Guba:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Administrative Information

Note: The numbers in round brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see https://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Trial Registration (2)

This study was registered under the German Clinical Trials Register number DRKS00035308, October 16th, 2024 (https://www.drks.de/DRKS00035308), with recruitment commencing in October 2024.

Protocol Version (3)

The protocol version number is 2.1, dated: January 11, 2025.

Ethics Approval and Consent to Participate (24)

The TRANSMIT study was approved by the Ethics Committee of the LMU Munich and is registered with the number 23–0921.

Consent for Publication

All authors have read and agreed to the published version of the manuscript.

Availability of Data and Material (29)

The TRANSMIT steering committee, including the trial biostatistician, has full access to the trial data. Any data required to support the protocol can be supplied on request.

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Declaration of Competing Interest (28)

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of Abbreviations

AE	Adverse event
AFP	Alpha-fetoprotein
BL	Baseline
CEA	Carcinoembryonic antigen
CRC	Colorectal cancer
CT	Computer tomography
DFS	Disease-free survival
DMC	Data monitoring committee
DSO	German Organ Transplantation Foundation (Deutsche Stiftung Organtransplantation)
dMMR	Deficient mismatch repair
ECOG	Eastern Cooperative Oncology Group
dCRF	Electronic case report form
EVE	Everolimus
FDG	Fluordesoxyglucose
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HCC	Hepatocellular carcinoma
HPB	Hepatopancreatobiliary
HR	Hazard ratio
iCCC	Intrahepatic cholangiocarcinoma
ITT	Intention-to-treat
LM	Liver metastases
LT	Liver transplantation
MC	Milan Criteria
MMF	Mycophenolate mofetil
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability-high
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
phCCC	Perihilar cholangiocarcinoma
RE	Re-evaluation
SAE	Serious adverse event

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SC	Screening
TAC	Tacrolimus
V	Follow-up visits.
WHO	World Health Organization

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