

A study of topotecan and cyclophosphamide added to standard treatment for children with advanced retinoblastoma in Tanzania

Submission date 03/09/2026	Recruitment status Not yet recruiting	☒ Prospectively registered ☐ Protocol
Registration date 12/10/2026	Overall study status Ongoing	☐ Statistical analysis plan ☐ Results
Last Edited 10/09/2026	Condition category Cancer	☐ Individual participant data ☒ Record updated in last year

Plain English summary of protocol

Background and study aims

Retinoblastoma is a rare type of eye cancer that begins in the retina, the light-sensitive nerve tissue at the back of the eye. In high-income countries children with retinoblastoma are cured almost 100% of the time. In Africa most children with retinoblastoma are present with advanced disease; treatment options are limited to a protocol used for over 30 years with unacceptably high failure rates. More than 40% of children die as a result. This study aims to evaluate the impact of adding topotecan to standard treatment on the survival of children with advanced retinoblastoma.

Who can participate?

Children aged 0 to 18 years with stage 2 or 3 retinoblastoma

What does the study involve?

Participants are randomly allocated to one of two groups. Group A will receive standard chemotherapy: intravenous (IV) vincristine, etoposide, and carboplatin (VEC). Group B will receive the experimental treatment of alternating standard VEC as above and IV topotecan, IV cyclophosphamide and intrathecal (spinal) topotecan.

What are the possible benefits and risks of participating?

A participant may or may not benefit directly from taking part in this study. The additional treatment being studied may help control retinoblastoma and may improve the chance of survival. It may also help preserve the affected eye and, where possible, vision. However, these benefits are not guaranteed because the purpose of this study is to find out whether adding the study treatment to standard treatment provides better outcomes.

The participant will also receive careful medical follow-up during the study. The information collected from your child may help doctors improve treatment for children with advanced retinoblastoma in the future.

The study treatment involves chemotherapy medicines, which may cause side effects. These may include reduced blood cells, which can increase the risk of infection, anaemia, bruising or bleeding; fever; tiredness; nausea and vomiting; diarrhoea or constipation; loss of appetite; hair

loss; and mouth sores.

Cyclophosphamide may also affect the bladder and, depending on the dose and treatment received, may affect future fertility. Rarely, chemotherapy may cause serious or long-term health problems.

Because the study involves adding treatment to standard therapy, the participant may experience additional or more severe side effects than with standard treatment alone. There may also be risks that are not yet known.

The study team will closely monitor your child for side effects and will provide appropriate medical care if they occur. You should inform the study team about any new or unusual symptoms during the study.

Where is the study run from?

The study will be performed in three oncology hospitals in Tanzania including Muhimbili National Hospital, Kilimanjaro Catholic Medical Centre and Bugando Medical Centre

When is the study starting and how long is it expected to run for?

January 2027 to June 2032

Who is funding the study?

Velux Stiftung (Switzerland)

Who is the main contact?

Dr Trish Scanlan, drtrish@wearetlm.org

Contact information

Type(s)

Principal investigator, Public, Scientific

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Additional identifiers

Study information

Scientific Title

The Topcat Trial – a randomised controlled open-label Phase II trial investigating the survival benefit of adding topotecan/cyclophosphamide to standard therapy for advanced (stage 2 and 3) retinoblastoma in Tanzania

Acronym

Topcat

Study objectives

Ethics approval required

Ethics approval required

Ethics approval(s)

Approved 31/01/2025, National Institute for Medical Research Ethics Committee (3 Barack Obama Drive PO Box 9653 11101 Dar es Salaam, Dar es Salaam, 11103, Tanzania; +255 (0)22 2121400; ethics@nimr.or.tz), ref: NIMR/HQ/R.8a/Vol.IX/4804

Primary study design

Interventional

Allocation

Randomized controlled trial

Masking

Open (masking not used)

Control

Active

Assignment

Parallel

Purpose

Treatment

Study type(s)

Health condition(s) or problem(s) studied

Retinoblastoma

Interventions

For participants in Arm A:

The chemotherapy regimen consists of vincristine IV, etoposide IV, and carboplatin IV administered intravenously on Day 1 (D1). Vincristine is given at a dose of 1.5 mg/m² body surface area (BSA), with a maximum dose of 2 mg per dose, and is administered as a slow intravenous bolus over 2–3 minutes. It should be diluted in not less than 10 mL of 0.9% sodium chloride (NaCl), with particular caution regarding the risk of extravasation. Etoposide is administered intravenously at a dose of 300 mg/m² BSA on Day 1 as a 4-hour infusion, at a concentration of 0.4 mg/mL in 0.9% NaCl. Rapid infusion should be avoided because it may lead to a hypotensive crisis. Carboplatin is administered intravenously at a dose of 600 mg/m² BSA on Day 1 as a 1-hour infusion, at a concentration of 0.5 mg/mL in 5% dextrose (D5%) or dextrose-normal saline (DNS).

Before each treatment cycle, the absolute neutrophil count (ANC) should be greater than 1,000 /μL and the platelet count greater than 100,000/μL. Haemoglobin, renal function, liver function tests (LFTs), and magnesium levels should also be assessed and confirmed to be adequate

before treatment. Dose modifications are required according to age. For children younger than 6 months, 50% of the standard dose of each drug should be administered. For children aged 6–12 months, 75% of the standard dose of each drug should be administered. For children older than 12 months, no age-related dose modification is required.

For participants in Arm B:

The treatment regimen consists of topotecan and vincristine administered intravenously (IV) from Day 1 to Day 5 (D1–5), together with intrathecal (IT) topotecan administered on Day 1 of each treatment cycle. Topotecan IV is given at a dose of 1.5 mg/m² body surface area (BSA) daily on Days 1–5 as a 30-minute infusion. It is compatible with 5% dextrose or 0.9% sodium chloride (NaCl), with a final concentration of 25–50 µg/mL of topotecan. Vincristine is given at a dose of 1.5 mg/m² body surface area (BSA), with a maximum dose of 2 mg per dose, and is administered as a slow intravenous bolus over 2–3 minutes. It should be diluted in not less than 10 mL of 0.9% sodium chloride (NaCl), with particular caution regarding the risk of extravasation. Intrathecal topotecan is administered as a bolus on Day 1 of each treatment cycle, with the dose determined by age. Children older than 3 years receive 0.4 mg, those older than 2 years but younger than 3 years receive 0.32 mg, and children younger than 2 years receive 0.25 mg. The drug is diluted with preservative-free sodium chloride (NaCl) to a final volume of 3 mL. Before each treatment cycle, the absolute neutrophil count (ANC) should be greater than 1,000 /µL and the platelet count greater than 100,000/µL. Haemoglobin, renal function, liver function tests (LFTs), and magnesium levels should also be assessed and confirmed to be adequate before treatment. For IV chemotherapy, age-related dose modifications apply. Children younger than 6 months should receive 50% of the standard dose of each drug, while those aged 6–12 months should receive 75% of the standard dose of each drug. For children older than 12 months, no age-related dose modification is required.

Note: G-CSF will be given as routine in study arm B and when required in the standard treatment arm A.

This is not a blind study and the chemotherapy handling used does not need any exceptional training beyond an understanding of its reconstitution and storage needs. As such the chemotherapy will be reconstructed, labeled and dispensed as normal by the local oncology pharmacy team following training by the study pharmacist from each site. It will be administered by the local nursing team following training by the study nurse from each site.

Schedules:

Children with stage 2 disease (microscopic extra-ocular disease) cannot be confirmed (and hence eligibility established) until after enucleation surgery. As a result, all children with stage 2 will receive 0-2 cycles (decided by the local ophthalmologist) of standard neoadjuvant (before enucleation) VEC (Vincristine IV, Etoposide IV, Cyclophosphamide IV) chemotherapy (followed by enucleation). If histopathology subsequently confirms stage 2 (stage 1 are excluded from trial at this stage), they will then be consented to join the trial and randomized to receive 12 cycles (in total) of either Arm A - standard VEC alone, or Arm B, receive alternating VEC (6 cycles) and TopC, (IV topotecan, IV cyclophosphamide and intrathecal topotecan 6 cycles) adjuvant therapy (after enucleation).

Children with stage 3 disease, which can be diagnosed at first presentation (without waiting for surgery, by simple clinical examination or through radiological assessment), will be consented and randomized up front to receive either standard chemotherapy (Arm A) or alternating cycles of VEC and TopC (Arm B) both before and after enucleation, (4 to 6 cycles of chemotherapy neoadjuvant as per the ophthalmology decision, and a total of 12 cycles of chemotherapy between pre- and post-operative chemotherapy).

The stage of the disease for each child will be determined at diagnosis through clinical, radiological (CT or MRI brain) and laboratory assessment (cerebrospinal fluid (CSF) cytospin and Bone marrow analysis). Children will then follow up clinically and with CSF analysis every 3 weeks throughout their treatment and every 3 months thereafter with clinical review and examination under anaesthetic (EUA) of fellow eye (+/-CSF cytospin analysis as clinically indicated) for a total of 2 years.

Study drug accountability (drug name – topotecan):

Receiving investigational drug shipments:

Upon receiving the investigational topotecan shipments, study personnel will check the shipment to ensure the contents are intact, comparing the invoice to the lot number, expiration date, quantity, and dosage of topotecan, and report any discrepancies immediately to the sponsor. The accurate receipt of the drug is essential for ensuring the integrity of the trial.

Storing study drug:

To maintain the efficacy and safety of topotecan during the study, it will be stored according to the manufacturer's specifications. If topotecan is in solution form, it must be refrigerated at a temperature of 2 to 8. If the drug is in its powder form, it should be stored at room temperature, away from light and moisture, in a tightly closed container. The drug will be securely locked in a designated, temperature-controlled area specified for paediatric chemotherapy medications. Temperature logs will be maintained to ensure topotecan is stored under the required conditions throughout the duration of the trial.

Dispensing according to clinical trial protocol:

During the study, topotecan will be administered to eligible participants according to the study protocol. The protocol provides detailed instructions on dosing, including dose modifications, administration, and how to manage potential side effects. Topotecan will be dispensed solely for the patients enrolled in the trial and should only be used by the assigned patient.

Reconstitution of topotecan will only be conducted by designated and trained clinical oncology pharmacists and will be dispensed by paediatric oncology nurses. Ensuring correct dispensing is critical for the accuracy and safety of the study.

Disposing of or returning drugs:

At the conclusion of the trial, topotecan that is unused or returned by participants will be disposed of, returned or used for patients as per the sponsor's instructions. Documentation will be maintained for all returned or disposed supplies, including the relevant protocol and drug identifiers, lot numbers, and quantities. Special care will be taken to distinguish between unopened drugs, unused doses from participants, and any broken or lost supplies. This process ensures that all study drug supplies are accurately accounted for and properly managed.

Inventory:

Throughout the study, investigators will track the availability of topotecan, ensuring that the drug supply is sufficient to meet patient treatment schedules while also monitoring expiration dates. If the stock levels falls below an estimated 4 month supply it will trigger the need to reorder the medication immediately to avoid any delays in treatment. If study drug is used for any other reason it will be recorded and reported and the medication will be replaced to ensure compliance with the trial protocol and maintain the validity of the study.

Randomization:

Sequence generation:

190 participants, 95 each arm, stage 2 and 3 Rb, will be randomized in a 1:1 ratio using a

computer-generated random sequence, with variable block size (4-8) and stratified by stage and by site. Randomization will be done in advance and there is a standard operating procedure for communication from the trial manager to the units on treatment allocation ensuring concealment of allocation.

Concealment mechanism:

Six different simple sealed envelope system accounts will be created, two for each study site. Each study site will have two simple sealed envelope randomization accounts, one for randomizing stage 2 retinoblastoma patients into standard VEC arm or topotecan arm and the other for randomizing stage 3 retinoblastoma patients into standard VEC arm or topotecan arm.

Each account will have 50 randomization chances for placing patients into arm A (standard arm: VEC) or arm B (treatment arm: topotecan). Each patient should be assigned a unique identification number (unique ID) which will be used as input for randomization protocol. The trial statistician will maintain a strict count of the total number of individuals in the study so that the study does not over-recruit. This will involve emailing sites when the study has recruited 180 individuals to the fact that only 10 more children should be recruited.

In case of uncertainties, whereby a person who will be managing patients' randomization procedures will not be available, the tossing of coin will be used instead.

In either of the stages, 2 or 3, when the coin is tossed after a patient being assigned a unique ID; if the head appears a patient will be placed to arm B (a treatment arm: topotecan) and if the tail appears a patient will be placed to arm A (a standard arm: VEC).

Allocation implementation:

Randomization forms will be available to each study site, of which prior information of recruited patients including patient initials, disease stage, recruited sites, hospital (site) given id as well as study number of patients. The forms will be then sent to a statistician for randomization. After randomization the forms will be sent back to recruiter who will have to update all details including prior information and randomized group of patients into randomization log (excel sheet) for keeping records. This study is open label so there is no need for a procedure for breaking the code.

Intervention Type

Drug

Phase

Phase III/IV

Drug/device/biological/vaccine name(s)

Topotecan, cyclophosphamide, vincristine, etoposide, carboplatin

Primary outcome(s)

1. Overall survival measured using the time from randomization to death from any cause. Participants who are alive at the end of the 24-month follow-up period or are lost to follow-up will be censored at the date they were last known to be alive.

Key secondary outcome(s)

1. Event-free survival (EFS), defined as the time from randomization to the first occurrence of any of the following events:

- 1.1. Death from any cause
- 1.2. Progressive disease
- 1.3. Resistant disease
- 1.4. Local recurrence
- 1.5. Central nervous system (CNS) recurrence
- 1.6. Distant recurrence
- 1.7. Treatment abandonment

Participants without an event at the end of follow-up will be censored at the date of their last disease assessment.

2. Progressive disease, defined as an increase in tumor burden, development of new local, regional, or metastatic disease, or radiologic or clinical evidence of disease progression during protocol therapy prior to completion of planned treatment.

3. Resistant disease, defined as failure to achieve adequate tumor regression following completion of planned neoadjuvant chemotherapy, resulting in disease that remains unsuitable for definitive surgical resection, as determined by the multidisciplinary treating team based on clinical examination and imaging findings.

4. Disease recurrence, classified as:

4.1. Local recurrence: recurrence of disease at the primary site following documented complete response, confirmed by ophthalmologic examination with supportive MRI or CT imaging, where indicated.

4.2. Central nervous system recurrence: recurrence involving the CNS confirmed by MRI (or CT when MRI is unavailable) and/or positive cerebrospinal fluid cytology.

4.3. Distant recurrence: development of metastatic disease outside the eye and CNS (including bone marrow, bone, lymph nodes, or other distant sites) confirmed by appropriate imaging and/or bone marrow examination.

The follow-up time for all outcomes will be 24 months (2 years). In the first year, patients will be followed up for every 3 months, and in the second year they will be followed up after every 6 months until the end of their follow up period. That is to say, in the first year they will be followed up 4 times but only 2 times in the second year.

For the case of serious adverse events and unexpected, serious adverse reactions will be reported to the study coordinating center within 24 hours of site awareness in accordance with study safety procedures.

Completion date

01/06/2032

Eligibility

Key inclusion criteria

1. Aged between 0 and 18 years
2. Willing to remain in the hospital if necessary and willing and able to return to the hospital for planned treatments and follow up assessments
3. A signed (or otherwise affirmed) informed consent document by the parent/guardian

Healthy volunteers allowed

No

Age group

Mixed

Lower age limit

0 Years

Upper age limit

18 Years

Sex

All

Total final enrolment

190

Key exclusion criteria

1. Patients with pre-existing chronic illnesses which require treatment may impact on the ability to tolerate chemotherapy or radiotherapy
2. Patients with a history of prior treatment
3. Patients with suspected or documented life-threatening infections (should be established before enrolment)
4. Patients with stage 3 disease who are enucleated up front

Date of first enrolment

01/01/2027

Date of final enrolment

30/06/2028

Locations**Countries of recruitment**

Tanzania

Sponsor information**Organisation**

London School of Hygiene & Tropical Medicine

ROR

<https://ror.org/00a0jsq62>

Funder(s)**Funder type****Funder Name**

Velux Stiftung

Alternative Name(s)

Velux Foundation

Funding Body Type

Private sector organisation

Funding Body Subtype

Trusts, charities, foundations (both public and private)

Location

Switzerland

Results and Publications

Individual participant data (IPD) sharing plan**IPD sharing plan summary**

Not expected to be made available