**CLINICAL STUDY PROTOCOL**

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| Protocol title | A multicentre, open-label, Phase 3, randomised controlled trial of duvelisib versus investigator's choice of gemcitabine or bendamustine in patients with relapsed/refractory nodal T cell lymphoma with T follicular helper (TFH) phenotype (TERZO) |

## Inclusion Criteria

Patients eligible for inclusion in this study must fulfil all of the following criteria:

1. ≥ 18 years of age at the time of signing informed consent
2. Pathologically confirmed nodal T cell lymphoma with TFH phenotype according to the criteria of the World Health Organization classification (Swerdlow 2017, Alaggio 2022) including any one of AITL, follicular T cell lymphoma, and other nodal peripheral T cell lymphoma (PTCL) with a TFH phenotype

   Note: Local pathology report should be reviewed by the medical monitor prior to randomisation; Slides, including positive staining for at least 2 TFH-related antigens (CD279/PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5), should be submitted for central pathology review; central pathology review is not required prior to initiation of treatment.
3. Relapsed or refractory to at least 1 prior systemic, cytotoxic therapy for T cell lymphoma
4. Measurable disease as defined by Lugano 2014 criteria (Cheson 2014) for T cell lymphoma

   Note: confirmation of measurable disease by central review or by medical monitor is required prior to randomisation.
5. Must have the following baseline organ function (without transfusion support within 30 days of C1D1) as defined by the following laboratory parameters:

| **Laboratory Parameter** | **Cut-off** |
|---|---|
| ***Haematology*** | |
| Haemoglobin | ≥ 8.0 g/dL (without transfusion support) |
| Platelet count | ≥ $50 \times 10^9$/L |
| Absolute neutrophil count (ANC) | ≥ $1.0 \times 10^9$/L (without growth factor support for ≥7 days for filgrastim and ≥14 days for pegylated growth factors) |
| CD4 lymphocyte count | ≥ 50/mm$^3$ ($0.05 \times 10^9$/L) |
| ***Renal*** | |

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| Serum creatinine | ≤ 2.0 × the upper limit of normal (ULN) or creatinine clearance ≥ 30 mL/min (estimated by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] or Cockcroft-Gault equation or measured) |
| ***Liver*** | |
| Total bilirubin | ≤ 1.5 × ULN (patients with documented Gilbert's syndrome may have a bilirubin > 1.5 × ULN but ≤ 3 × ULN) |
| ALT | ≤ 2.5 × ULN |
| AST | ≤ 2.5 × ULN |

6. ECOG performance status ≤ 2
7. Recovery to Grade ≤ 1 or baseline for any non-haematologic toxicities due to prior treatments, except for peripheral neuropathy (Grade ≤ 2) or alopecia
8. Washout of at least 14 days or 5 half-lives, whichever is longer, from any prior T cell lymphoma-directed therapy (including approved and investigational therapies) to the first dose of study drug (14 days for radiation therapy)
9. For women of childbearing potential (WOCBP): negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test within 3 days before first treatment
10. Note: A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A woman is considered postmenopausal if she has had no menses for 12 months without an alternative medical cause.Male and female patients of reproductive potential must be willing to use a highly effective method* of contraception for the duration of study treatment and for the defined period following the last dose of the investigational medicinal product (IMP) listed below, unless a longer period is specified in the manufacturer's SmPC:

| **Study Treatment** | **Males** | **Female** |
|---|---|---|
| Duvelisib** | 3 months | 3 months |
| Gemcitabine | 6 months | 6 months |
| Bendamustine | 6 months | 6 months |
| * Methods of contraception are described in Appendix 2.<br>** Participants who are taking duvelisib must also use a secondary form of contraception as it is unknown if duvelisib may reduce the effectiveness of hormonal contraception. | | |

11. Signed and dated institutional review board (IRB)/independent ethics committee (IEC)/central ethics committee (CEC)-approved informed consent form before any screening procedures are performed

## 1.1 Exclusion Criteria

Patients are to be excluded from the study if they meet any of the following criteria:

1. Cutaneous-only disease
2. Received prior allogeneic transplant any time in the past or received autologous transplant within 60 days prior to the first dose of study drug
3. Received prior treatment with a phosphoinositide-3-kinase (PI3K) inhibitor
4. Prior exposure to planned study treatment investigator's choice therapy (gemcitabine or bendamustine) within 60 days prior to the first dose of study drug
5. Major surgery within 4 weeks prior to the first dose of study drug and/or expected major surgical intervention while receiving study treatment
6. Any known history of or current central nervous system involvement by T cell lymphoma
7. Patients with a known history of human immunodeficiency virus (HIV) seropositivity or history of active or latent hepatitis B or C. Patients with cured hepatitis C and/or serology consistent with hepatitis B immunity are not excluded from the study.

   Note: Patients with a positive hepatitis B surface antigen [HBsAg] or hepatitis C antibody [HCVAb] in the absence of documented cure will be excluded. Patients with a positive hepatitis B core antibody [HBcAb] must have negative hepatitis B virus [HBV] DNA to be eligible, must receive prophylaxis with entecavir [or equivalent] concomitant with duvelisib treatment, and must be periodically monitored for HBV reactivation by institutional guidelines.
8. Active cytomegalovirus (CMV) infection
9. History of tuberculosis treatment within 2 years prior to screening
10. History of chronic liver disease

    Note: Patients with non-alcoholic fatty liver disease (NAFLD) can be included if they meet the inclusion criteria for bilirubin, ALT, and AST.
11. Active uncontrolled alcohol or drug abuse that may impair compliance with study protocol.
12. Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids > 20 mg of prednisone (or equivalent) once daily. Note: chronic is defined as continuous treatment for at least 4 weeks.
13. Ongoing treatment for systemic bacterial, fungal, or viral infection at screening

    Note: Patients on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met
14. Administration of a live viral vaccine within 6 weeks of the first dose of study drug
15. Concurrent administration of medications or foods (e.g., grapefruit) that are strong inhibitors or inducers of CYP3A
16. Unable to receive prophylactic treatment for *Pneumocystis* at screening
17. Prior surgery or condition with gastrointestinal dysfunction that may significantly affect drug absorption (e.g., gastric bypass surgery, gastrectomy)

18. Female patients who are pregnant or breastfeeding
19. History of other malignancy that could affect compliance with the protocol or interpretation of results:
    - Patients with a history of curatively treated basal or squamous cell carcinoma or melanoma of the skin or in situ carcinoma of the cervix at any time prior to the study are eligible.
    - Patients with any malignancy appropriately treated with curative intent and the malignancy has been in remission without treatment for ≥ 2 years prior to enrolment are eligible.
    - Patients with low-grade, early-stage prostate cancer (Gleason score 6 or below, Stage 1 or 2) with no requirement for therapy at any time prior to study are eligible.
20. History of stroke, unstable angina, and/or myocardial infarction, within the last 6 months prior to screening, New York Heart Association Class 3 or 4 congestive heart failure, or an uncontrolled arrythmia
21. Unstable or uncontrolled medical condition (e.g., unstable cardiac function, unstable pulmonary condition, uncontrolled diabetes), including severe psychiatric disorder or any important medical condition or abnormal laboratory finding that would, in the investigator's judgement, increase the risk to the patient associated with his or her participation in the study
22. Known hypersensitivity to any of the study drugs or drug product ingredients
23. Concurrent participation in another interventional clinical trial
24. Eligible for high-dose therapy and subsequent allogeneic blood stem cell transplantation