A Multicenter, Open-Label, Phase 3, Randomized 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 Phenotype (TERZO)

Publication #: 3074.1
Topic: T Cell, NK Cell, or NK/T Cell Lymphomas: Clinical and Epidemiological

Kate Cwynarski,[1] Eva Domingo-Domenech,[2] David Sidransky,[3] Ohad Bentur,[4] Pier Luigi Zinzani[5]

[1]Department of Hematology, University College London Hospital, London, UK; [2]Catalan Institute of Oncology, Hospital Duran i Reynals, IDIBELL, Barcelona, Spain; [3]Johns Hopkins University, Baltimore, MD, USA; [4]Secura Bio, Inc, Las Vegas, NV, USA; [5]Institute of Hematology "Seràgnoli," University of Bologna, Bologna, Italy

ABSTRACT

- Peripheral T-cell lymphomas (PTCL) are a rare, heterogeneous group of aggressive lymphomas that represent 10%-15% of all non-Hodgkin lymphomas. Patients with newly diagnosed PTCL are commonly treated with anthracycline-based combination chemotherapy; however, the majority will develop relapsed/refractory (R/R) disease. Currently, no agent is approved in the EU or UK for treatment of patients with R/R PTCL, except brentuximab vedotin (BV) for anaplastic large-cell lymphoma (ALCL). Approvals of single agents for PTCL (except for BV) in the US were based on single-arm studies
- Primary nodal subtypes of PTCL make up the majority of PTCL in North America and Europe and include PTCL-not otherwise specified (NOS) (34%), angioimmunoblastic T-cell lymphoma (AITL) (16%-29%), and ALCL (16%-24%). The AITL cell of origin, a follicular helper T (T_{FH}) cell, has a set of recurrent gene mutations frequently found in cases of AITL and PTCL-NOS. Due to similarities in clinical, immunophenotypic, and genetic characteristics, the 5th edition of the World Health Organization (WHO) classification of lymphoid neoplasms groups AITL, PTCL-NOS with T_{FH} phenotype, and follicular T-cell lymphoma under the category nodal follicular helper T-cell lymphoma (nTFHL)
- Duvelisib, an oral inhibitor of phosphatidylinositol 3-kinase (PI3K)-δ and PI3K-γ isoforms, is approved in the US for the treatment of adult patients with R/R chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least 2 prior lines of systemic therapy with the following limitations of use: Duvelisib in the US is not indicated or recommended for the treatment of any patients with CLL or SLL as initial or second-line treatment due to an increased risk of treatment-related mortality. In 2019, the FDA issued an orphan drug designation to DUV for the treatment of T-cell lymphoma
- Duvelisib is authorized in the EU/UK as a monotherapy indicated for the treatment of adult patients with R/R CLL after at least 2 prior therapies and follicular lymphoma that is refractory to at least 2 prior systemic therapies. In January 2023, the European Commission issued an orphan drug designation to duvelisib for treatment of adult patients with PTCL
- In the PRIMO study (NCT03372057), outcomes with duvelisib in patients with R/R PTCL were objective response rate (ORR) 48.0%, median progression-free survival (mPFS) 3.45 months, and median overall survival (mOS) 12.35 months. In patients with AITL, considered the hallmark for T_{FH} lymphomas, outcomes were ORR 62.2%, mPFS 8.34 months, and mOS 18.07 months
- The TERZO™ study (NCT06522737; EU CT: 2024-516605-23-00) will evaluate efficacy and safety of duvelisib vs investigator's choice of gemcitabine (GEM) or bendamustine (BEN), 2 standard of care regimens commonly used in clinical practice in patients with R/R nTFHL
- TERZO is a multicenter, open-label, phase 3, randomized study expected to enroll 124 patients (at nearly 45 EU/UK sites) with R/R nTFHL who have progressed on ≥1 line of systemic anticancer therapy. Study duration will be 48 months; patients will be randomized 1:1 and stratified by number of prior therapies and AITL score
- Arm 1: duvelisib 75 mg orally twice daily (BID) for cycles 1 and 2, and duvelisib 25 mg BID for cycles 3+, in 28-day cycles. Arm 2: either GEM 1200 mg/m^2 intravenous (IV) on days 1, 8, and 15 of each 28-day cycle (up to 6 cycles) or BEN 90-120 mg/m^2 IV on days 1 and 2 of each 21-day cycle (up to 6 cycles)
- Primary endpoint: independent review committee (IRC)-assessed PFS; key secondary endpoint: OS; additional secondary endpoints: investigator (INV)-assessed PFS, ORR, complete response rate, duration of response (DOR), safety, quality of life, percentage of patients proceeding to stem cell transplant (SCT), and INV-assessed PFS in patients proceeding to SCT; exploratory endpoints: AITL vs non-AITL outcomes, whole exome sequencing, circulating DNA, AITL score
- Eligibility criteria include adults with R/R nTFHL, ≥1 prior line of systemic therapy, measurable disease, Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2, and no prior history of allogeneic SCT or PI3K inhibitor use
- DUV monotherapy has demonstrated activity in R/R PTCL, with more pronounced effect in AITL. TERZO will test the hypothesis that DUV monotherapy is associated with improved outcomes compared with GEM or BEN in patients with R/R nTFHL

RATIONALE FOR DUVELISIB IN R/R NODAL T-CELL LYMPHOMA WITH T_{FH} SUBTYPE

Phase 2 PRIMO Study

NCT03372057

Patients with R/R PTCL
- Pathologically confirmed PTCL subtypes per WHO classification
- Measurable disease per Lugano 2014 criteria
- No prior history of allogeneic SCT or treatment with PI3K inhibitor
- ECOG PS ≤2

Dose Optimization Phase
- Cohort 1: Duvelisib 25 mg po BID start (n=20)
- Cohort 2: Duvelisib 75 mg po BID start (n=13)

Dose Expansion Phase (N=123 enrolled)

Primary endpoint (dose expansion phase)	IRC-assessed ORR
Secondary endpoints	Safety, DOR, PFS, DCR (CR + PR + SD ≥8 weeks), OS, PK
Exploratory endpoints	PD and biomarkers

CR, complete response; CT, computed tomography; DCR, disease control rate; PD, progressive disease; PET, positron emission tomography; PK, pharmacokinetics; po, by mouth; PR, partial response; SD, stable disease.

Eligible patients had to have ≥2 cycles of standard regimen and failed to achieve PR or better after ≥2 cycles or failed to achieve CR after completion of standard therapy or progressed after initial response. Each cycle was 28 days.
An eligibility criterion of a CD4 lymphocyte count ≥50/mm^3 was added for the dose expansion phase.
Pneumocystis jirovecii prophylaxis was required; herpes simplex and varicella zoster virus prophylaxis were indicated as needed.

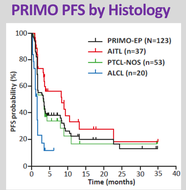
- In patients with AITL, considered the hallmark for T_{FH} lymphomas, outcomes were ORR 62.2%, mPFS 8.34 months, and mOS 18.07 months
- Adverse events were generally manageable with per-protocol dose modifications and were consistent with those observed previously

PRIMO Efficacy Outcomes in the AITL Subgroup

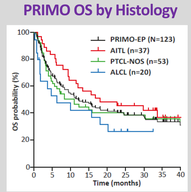
Efficacy outcomes	PRIMO (AITL only) (n=37)
ORR, %	62.2
CR, %	51.4
PR, %	11
Median DOR (95% CI), mo	11.70 (7.29, NC)
Median PFS (95% CI), mo	8.34 (3.68, 13.34)
Median OS (95% CI), mo	18.07 (9.56, NC)

CR, complete response; mo, month; NC, not calculated; PR, partial response.

PRIMO PFS by Histology



PRIMO OS by Histology



PRIMO Adverse Events of Special Interest

Adverse event of special interest	PRIMO-EP (N=123)	
	Any grade, n (%)	Grade ≥3, n (%)
Alanine/aspartate aminotransferase elevation	55 (44.7)	30 (24.4)
Infections*	51 (41.5)	16 (13.0)
Cutaneous reactions	44 (35.8)	13 (10.6)
Diarrhea	41 (33.3)	12 (9.8)
Neutropenia	41 (33.3)	22 (17.9)
Pneumonia	8 (6.5)	5 (4.1)
Pneumonitis	2 (1.6)	1 (0.8)
Colitis	4 (3.3)	2 (1.6)

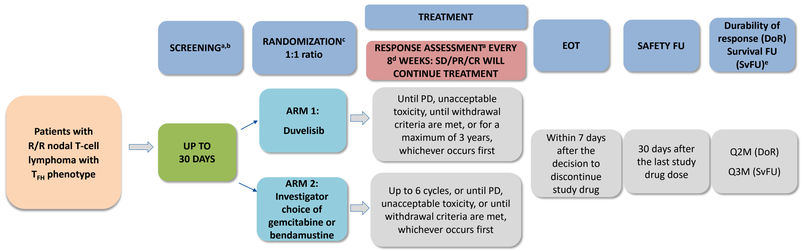
*There were no cases of *Pneumocystis jirovecii* pneumonia in study.

Outcomes From Other Trials

	BENTLY	IC arm in phase 3 studies	
	Bendamustine (N=55)	ORACLE (Azacitidine vs IC in R/R T_{FH} PTCL)	LUMIERE (Alisertib vs IC in R/R PTCL)
N in IC arm	N/A	44 (24 gemcitabine, 16 bendamustine, 4 romidepsin)	30 gemcitabine (23 evaluable for efficacy)
Disease type	PTCL-NOS: 38% AITL: 53%	AITL/T_{FH}: 100% (93% confirmed)	PTCL-NOS: 50% AITL: 27% ALCL: 3%
Median PFS, mo	3.6	2.8	1.9
Median OS, mo	6.2	10.3	12.0*

IC, investigator choice; mo, month.
*For the full IC arm with 133 patients (30 gemcitabine, 80 pralatrexate, 23 romidepsin).

TERZO STUDY SCHEMA



CR, complete response; EOT, end of treatment; FU, follow-up; PD, progressive disease; PR, partial response; SD, stable disease; Q2M, every 2 months; Q3M, every 3 months.
[a] Bone marrow assessments are optional.
[b] Central pathology review: As part of the patient's medical history, pathology reports from the time of diagnosis are to be collected. In addition, stained formalin-fixed, paraffin-embedded (FFPE) slides used for nodal T-cell lymphoma with T_{FH} phenotype diagnosis must be collected for all screened patients and submitted for central pathology review.
[c] Randomization will be stratified by AITL score (0-2 vs 3-4) and number of prior lines of therapy for T cell lymphoma (1 vs >1).
[d] Every 6 weeks for bendamustine.
[e] SvFU: patients with PD at EOT; DoR followed by SvFU: patients with no PD at EOT.

ELIGIBILITY CRITERIA

Key inclusion criteria	Key exclusion criteria
• Pathologically confirmed nodal T-cell lymphoma with T_{FH} phenotype according to WHO classification, including: – AITL – Follicular T-cell lymphoma – Other nodal PTCL with a T_{FH} phenotype • R/R to at least 1 prior systemic, cytotoxic therapy for T-cell lymphoma • Measurable disease as defined by Lugano 2014 criteria (Cheson 2014) for T-cell lymphoma	• Cutaneous-only disease • Received prior allogeneic transplant any time in the past or received autologous transplant within 60 days prior to the first dose of study drug • Received prior treatment with a PI3K inhibitor or prior exposure to planned study treatment investigator's choice therapy (gemcitabine or bendamustine) within 60 days of the first dose of study drug

STUDY ENDPOINTS*

Primary endpoint	• IRC-assessed PFS
Key secondary endpoint	• OS
Secondary endpoints	• INV-assessed PFS • IRC-assessed ORR • IRC-assessed complete response rate • IRC-assessed DOR • Percentage of patients proceeding to SCT • INV-assessed PFS in patients proceeding to SCT • Patients with adverse events • Quality of life scores (EORTC QLQ-C30, EQ-5D-5L, EORTC QLQ-NHL-HG29)
Exploratory endpoints	• AITL vs non-AITL outcomes • Whole exome sequencing • Circulating DNA • AITL score (β2M, age, CRP, ECOG PS)

CRP, C-reactive protein; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
*Disease and response assessment include 18F-FDG–PET/CT, PET-CT (CT images with PET should be diagnostic with contrast wherever possible), 5-point scale (Lugano classification), and Lugano 2014 response criteria for malignant lymphoma. Where PET-CT is not feasible, CT with contrast or MRI may be used. Subsequently, for FDG-avid PTCL, PET-CT will be used to assess disease status and for FDG–non-avid PTCL, CT with contrast or MRI will be appropriate substitutes. Safety assessments include vital signs, height (at screening only), weight, physical examination, 12-lead electrocardiograms, ECOG PS, *Pneumocystis jirovecii* pneumonia prophylaxis review, adverse events monitoring, and laboratory values.

STUDY DURATION AND SCHEDULE OF ADMINISTRATION

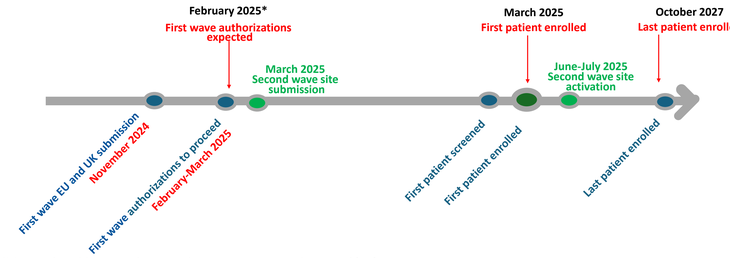
Study Duration
- Patients in the duvelisib arm will receive treatment until progressive disease (PD), unacceptable toxicity, until withdrawal criteria are met, or for a maximum of 3 years, whichever occurs first
- Patients in the investigator's choice arm will receive treatment for up to 6 cycles (gemcitabine: 28-day cycles; bendamustine: 21-day cycles) or until PD, unacceptable toxicity, or until withdrawal criteria are met, whichever occurs first
- All patients may be followed for up to 3 years after randomization
- The duration of individual participation will be approximately 24 months

Schedule of Administration

Arm 1
- Cycles 1 and 2:
  Duvelisib 75 mg orally BID in 28-day cycles
- Cycles 3+:
  Duvelisib 25 mg orally BID in 28-day cycles

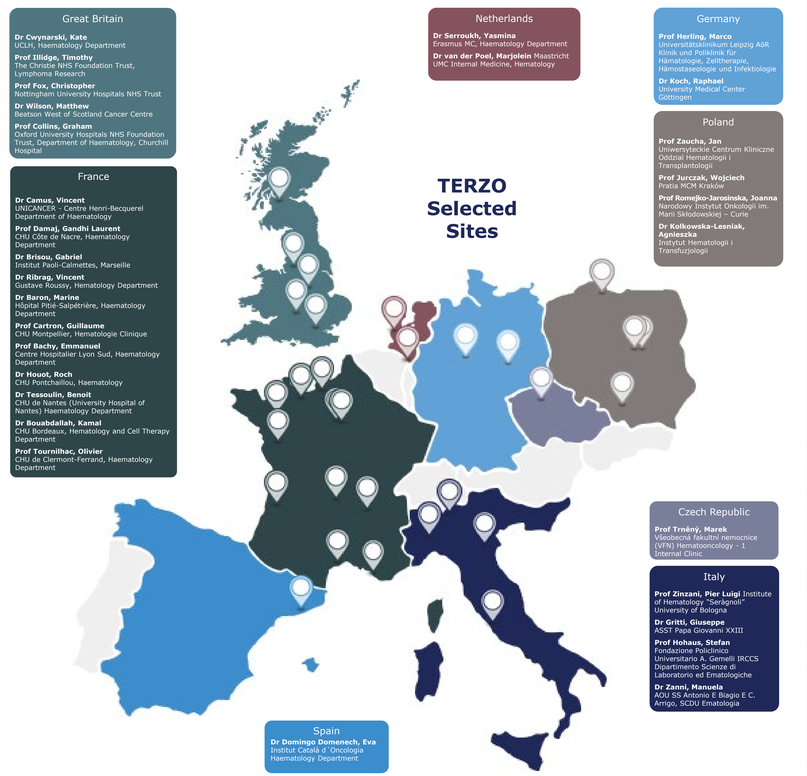
Arm 2
One of the following:
- **Gemcitabine 1200 mg/m^2** IV over 30 minutes on days 1, 8, and 15 of 28-day cycle for up to 6 cycles
- **Bendamustine 90-120 mg/m^2** IV over 30 minutes on days 1 and 2 of 21-day cycle for up to 6 cycles

PROJECT TIMELINE



***Medicines and Healthcare products Regulatory Agency approval expected (UK).**

STUDY SITES AND INVESTIGATORS



REFERENCES

1. Attygalle AD. *Diagn Histopathol.* 2018;24(7):227-236. 2. COPIKTRA. Package insert. Secura Bio, Inc; 2024. 3. COPIKTRA. Summary of Product Characteristics. Secura Bio, Ltd; 2021. 4. Damaj G et al. *J Clin Oncol.* 2013;31(1):104-110. 5. d'Amore F et al. *Ann Oncol.* 2015;26(suppl 5):v108-v115. 6. Data on file, Secura Bio, Inc. 7. Dupuis J et al. *Lancet Haematol.* 2024;11(6):e406-e414. 8. Horwitz SM et al. *Blood.* 2018;131(8):888-898. 9. O'Connor OA et al. *J Clin Oncol.* 2011;29(9):1182-1189. 10. O'Connor OA et al. *J Clin Oncol.* 2015;33(23):2492-2499. 11. O'Connor OA et al. *J Clin Oncol.* 2019;37(8):613-623. 12. Vose J et al. *J Clin Oncol.* 2008;26(25):4124-4130.

CONTACT INFORMATION

For TERZO study inquiries, please contact Secura Bio, Inc. Medical Information: terzostudy@securabio.com

FOR FURTHER INQUIRIES OR INFORMATION ABOUT THE TERZO STUDY, PLEASE SCAN QR CODE