A Multicenter, Open-Label, Phase 3, Randomized Controlled Trial of Duvelisib vs Investigator's Choice of Gemcitabine or Bendamustine in Patients With Relapsed/Refractory Nodal T-Cell Lymphoma With T Follicular Helper Phenotype (TERZO™)

Poster: TCL-136

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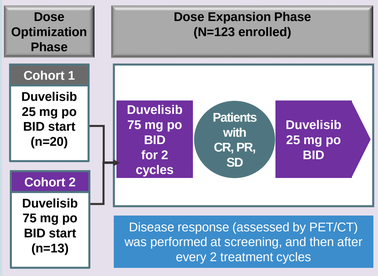
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Introduction

- The angioimmunoblastic T-cell lymphoma (AITL) cell of origin, a T-follicular helper (TFH) cell, has a set of recurrent mutations frequently found in AITL and some cases of peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS)[1]
  - The similarities in clinical, immunophenotypic, and genetic characteristics have led to a reclassification in the 5th edition of the World Health Organization (WHO) classification of lymphoid neoplasms, grouping AITL, PTCL-NOS with TFH phenotype, and follicular T-cell lymphoma together under the term nodal TFH lymphoma (nTFHL)[1]
- Duvelisib is an oral inhibitor of phosphatidylinositol 3-kinase-δ and -γ. US indications: adults with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after ≥2 prior lines of systemic therapy. Duvelisib is not indicated or recommended for the treatment of any patients with CLL/SLL as initial or second-line treatment due to increased risk of treatment-related mortality. EU/UK indications: adults with R/R CLL after ≥2 prior therapies and for follicular lymphoma that is refractory to ≥2 prior systemic therapies. The use of duvelisib in PTCL is investigational[2,3]
- In the phase 2 PRIMO study (NCT03372057), duvelisib in R/R PTCL outcomes were overall response rate (ORR) 48.0%, median progression free survival (mPFS) 3.4 mo, median overall survival (mOS) 12.4 mo. AITL subgroup outcomes were ORR 62.2%, complete response 51.4%, mPFS 8.3 months, and mOS 18.1 months[4]
- TERZO (NCT06522737; EU CT: 2024-516605-23-00) is a multicenter, open-label, phase 3, randomized study that will evaluate efficacy and safety of duvelisib vs investigator's choice of gemcitabine (GEM) or bendamustine (BEN). TERZO is expected to enroll 124 patients 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. Primary endpoint: Independent Review Committee–assessed PFS (Lugano 2014 criteria); key secondary endpoint: OS
- Duvelisib monotherapy has demonstrated activity in patients with R/R PTCL, with more pronounced effect in AITL (TFH cell-of-origin). TERZO will test the hypothesis that duvelisib 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 TFH Subtype

PRIMO Study Schema (Phase 2)



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

BID, twice daily; CR, complete response; CT, computed tomography; DCR, disease control rate; DOR, duration of response; IRC, independent review committee; 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.

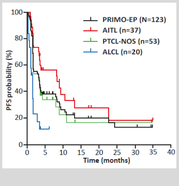
- In patients with AITL, considered the hallmark for TFH lymphomas, outcomes were ORR 62.2%, mPFS 8.34 months, and mOS 18.07 months
- Adverse events were generally manageable with per-protocol dose modifications and were consistent with those observed previously

PRIMO Efficacy Outcomes in the AITL Subgroup

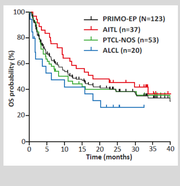
Efficacy outcomes	PRIMO (AITL only) (n=37)
ORR, %	62.2
CR, %	51.4
PR, %	11
Median DOR (95% CI), mo	11.70 (7.29, NC)
mPFS (95% CI), mo	8.34 (3.68, 13.34)
mOS (95% CI), mo	18.07 (9.56, NC)

CR, complete response; DOR, duration of 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 (%)
ALT/ AST 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)

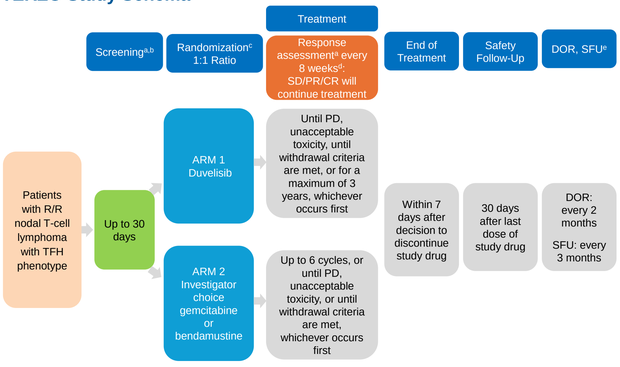
ALT, alanine aminotransferase; AST, aspartate aminotransferase.
*There were no cases of *Pneumocystis jirovecii* pneumonia in study.

Outcomes From Other Trials[5-7]

	BENTLY	IC arm in phase 3 studies	
	BEN (N=55)	ORACLE (Azacitidine vs IC in R/R TFH PTCL)	LUMIERE (Alisertib vs IC in R/R PTCL)
N in IC arm	N/A	44 (24 GEM, 16 BEN, 4 romidepsin)	30 GEM (23 evaluable for efficacy)
Disease type	PTCL-NOS: 38% AITL: 53%	AITL/TFH: 100% (93% confirmed)	PTCL-NOS: 50% AITL: 27% ALCL: 3%
mPFS, mo	3.6	2.8	1.9
mOS, mo	6.2	10.3	12.0*

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

TERZO Study Schema



CR, complete response; DOR, durability of response; PD, progressive disease; PR, partial response; SD, stable disease; SFU, survival follow-up.
[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 slides used for nodal T-cell lymphoma with TFH 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] SFU: patients with PD at end of treatment; DOR followed by SFU: patients with no PD at end of treatment.

TERZO Eligibility Criteria

Key inclusion criteria	Key exclusion criteria
• Pathologically confirmed nodal T-cell lymphoma with TFH phenotype according to WHO classification, including: – AITL – Follicular T-cell lymphoma – Nodal PTCL with a TFH 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

TERZO 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)

β2M, beta-2-macroglobulin; CRP, C-reactive protein; CT, computed tomography; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG, fluorodeoxyglucose; INV, investigator; IRC, independent review committee; MRI, magnetic resonance imaging; PET, positron emission tomography; PI3K, phosphatidylinositol 3-kinase; SCT, stem cell transplant.
[a]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.

TERZO Study Duration and Schedule of Administration

Study Duration

- Patients in the duvelisib arm will receive treatment until 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

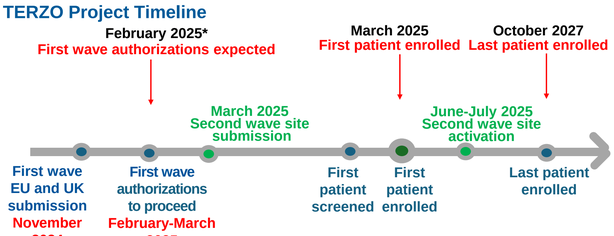
Schedule of Administration

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/m²** IV over 30 minutes on days 1, 8, and 15 of 28-day cycle for up to 6 cycles
- **Bendamustine 90-120 mg/m²** IV over 30 minutes on days 1 and 2 of 21-day cycle for up to 6 cycles

BID, twice daily; IV, intravenous; PD, progressive disease.

TERZO Project Timeline



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

Study Sites and Investigators

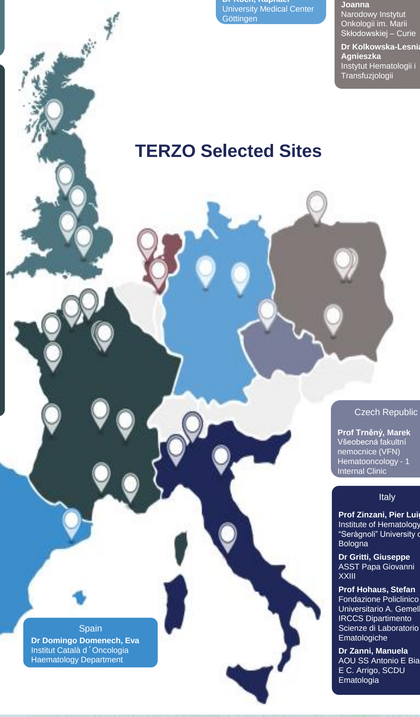
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References

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