Preliminary results from an open-label, phase II study of tipifarnib in relased or refractory peripheral T-cell lymphoma.

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INTRODUCTION

Tipifarnib:

- Potent and highly selective **inhibitor** of **Farnesyl Transferase**
- Previously studied in > 5,000 patients (pts)
- Previous trials without genetic selection yielded insufficient clinical activity to support registration, though evidence of single agent activity had been reported.
  - 41% response rate (7 responses out of 17 pts) in patients (pts) with T-cell Non-Hodgkin Lymphoma, including 4 objective responses in 8 pts with peripheral T-cell lymphoma (PTCL)[1]
- Manageable safety profile as single agent therapy (<25% treatment discontinuation).

OBJECTIVES

- This is a Phase 2 study designed to investigate the antitumor activity of tipifarnib in 18 pts with relapsed or refractory PTCL.
- **Primary Objective**: ORR by IWC and/or mSWAT
- **Secondary Objectives:** PFS, DOR, safety/tolerability
- **Exploratory Objectives:** Biomarkers

METHODS

Study Design

- Tipifarnib 600 mg orally twice daily on Days 1 – 7 and 15 – 21 in 28-day cycles
- Simon 2-stage design for ORR
  - Stage 1: Need 2 CR/PRs in first 11 pts
  - Stage 2: If Stage 1 criteria met, enroll 7 pts
  - For 10% (H0) vs 30% (H1) ORR, targeting ≥ 4 CR/PRs out of 18

Key Eligibility Criteria

- Diagnosis of PTCL including:
  - Anaplastic large cell lymphoma (ALCL), ALK positive
  - ALCL, ALK negative
  - Angioimmunoblastic T-cell lymphoma (AITL)
  - Enteropathy-associated T-cell lymphoma
  - Extranodal natural killer (NK) T-cell lymphoma, nasal type
  - Hepatosplenic T-cell lymphoma
  - PTCL, no otherwise specified (NOS)
  - Subcutaneous panniculitis-like T-cell lymphoma
- Relapsed or are refractory to at least 1 prior systemic cytotoxic therapy.

AITL Expansion Cohort:

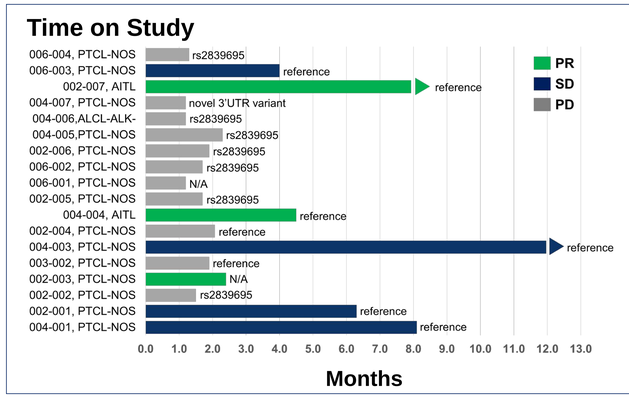
- Based on observed antitumor activity in stages 1 and 2, an AITL expansion cohort (N = 12) is currently enrolling.

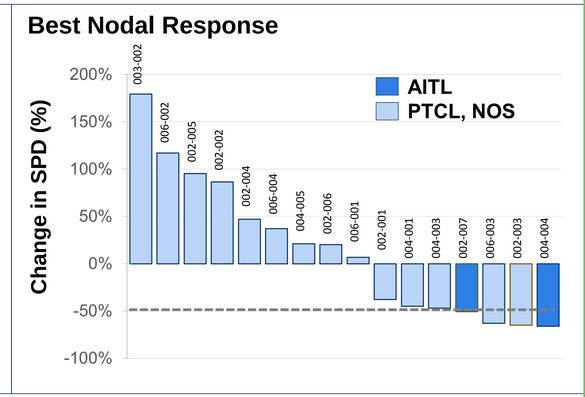
Clinical trial information: NCT02464228.

RESULTS

Results based on preliminary data as of May 2017.

N = 18	N (%)
Age, median (range)	**67 years (31 – 88)**
Gender	
Female	**4 (22)**
Male	**14 (78)**
PTCL Subtype	
AITL	**2 (11)**
ALCL, ALK negative	**1 (6)**
PTCL, NOS	**15 (83**
Number of prior therapies, median (range)	**4 (1 – 7)**

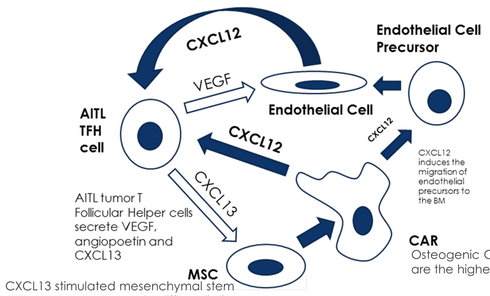




Toxicities

- Toxicities were consistent with known safety profile of tipifarnib. No patient discontinued due to AEs.
- Grade ≥ 3 TEAEs occurring in > 10% of pts were hematology-related and included neutropenia (83%), thrombocytopenia (61%), leukopenia (50%), anemia (39%), febrile neutropenia (33%) and lymphopenia (17%).
- Myelosuppression was manageable with treatment interruption, dose reductions and/or growth factor support.
- Starting dose was reduced from 900 mg to 600 mg based on the observed tolerability profile in stage 1.

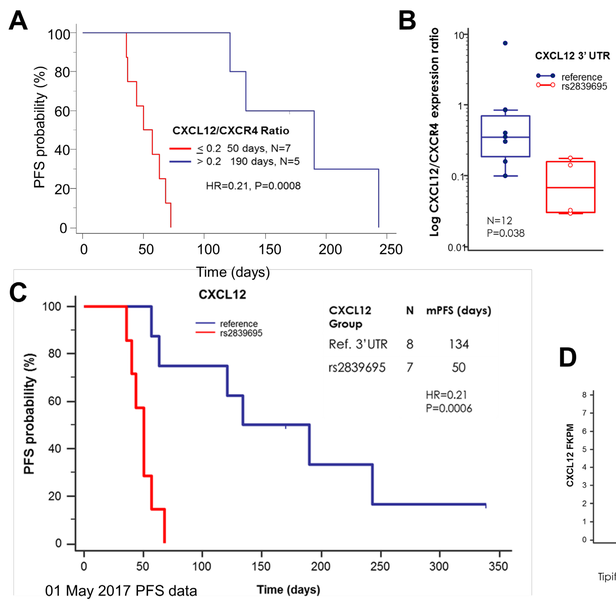
RESPONSES IN AITL MAY BE ASSOCIATED WITH HIGH CXCL12 SECONDARY TO CXCL13 SECRETION AND ANGIOGENESIS



Two main origins of CXCL12 in AITL:

1. **AITL secrete proangiogenic factors that stimulate the production of CXCL12 by vascular endothelial cells** [2, 3]
2. **CXCL13 secreted by AITL tumor cells upregulates CXCL12 in mesenchymal cells through inhibition of miR23** [4, 5]

CXCL12 EXPRESSION AND 3'UTR GENE VARIATION AS POTENTIAL BIOMARKERS OF TIPIFARNIB'S ACTIVITY IN PTCL



A. PFS in high (blue) vs low (red) tumor CXCL12 expressing PTCL (n=12 samples analyzed by RNASeq)
B. CXCL12 expression in reference (blue) vs 3'UTR CXCL12 gene variant (red) PTCL
C. PFS in reference (blue) vs 3'UTR CXCL12 gene variant (red) PTCL (n=15 samples analyzed by NGX)
D. CXCL12 is expressed in Tipifarnib sensitive TLL cell lines
E. Tipifarnib IC50 is lower in TLL cell lines with higher CXCL12 expression

CONCLUSIONS

- **These preliminary data indicate that tipifarnib has antitumor activity, particularly in pts with AITL histology, with high levels of CXCL12 gene expression and absence of 3'UTR CXCL12 gene variation.**
- **Tipifarnib was generally well-tolerated. Most common treatment-related AEs (grade ≥ 3) were myelosuppression, including neutropenia, thrombocytopenia and leukopenia.**
- **The phase 2 study has been extended to enroll an additional 12 pts with AITL aimed at confirming the preliminary observations and validating CXCL12 as a biomarker of tipifarnib activity.**

REFERENCES

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