Tipifarnib in Relapsed or Refractory Angioimmunoblastic T-cell Lymphoma (AITL) and CXCL12+ Peripheral T-cell Lymphoma (PTCL): Preliminary Results from an Open-Label, Phase 2 Study

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BACKGROUND

Tipifarnib:

- Potent and highly selective **inhibitor** of **Farnesyl Transferase (FT)** and enzyme which catalyzes post-translational attachment of farnesyl groups required for localization of signaling molecules to the inner cell membrane.
- Prior activity of tipifarnib has been reported in squamous tumors that carry mutant HRAS (Ho 2018), a farnesylated oncoprotein, as well as in lymphoid (Witzig 2011), myeloid and solid tumors (pancreatic cancer, breast) that do not carry HRAS mutations (Pass 2018).
- No molecular mechanism of action had previously been determined that could explain the clinical activity of tipifarnib across a range of diverse clinical indications.

CXCL12

- Chemokine, also known as Stroma Derived Factor 1 (SDF1), which is essential for T cell homing to lymphoid organs and the bone marrow and for maintenance of immune cell progenitors.
- CXCL12 drives the homing and growth of tumors expressing its corresponding extracellular receptor CXCR4. Preliminary data suggested the CXCL12 pathway may be a target of tipifarnib in CXCR4 expressing tumors (Witzig 2017, Gualberto 2017).

METHODS

This Phase 2 study was designed to investigate the antitumor activity of tipifarnib in pts with relapsed or refractory PTCL. After preliminary data suggested that CXCL12 expression was associated with clinical activity, two expansion cohorts were added to enroll subjects with tumors expected to overexpress CXCL12: AITL, and PTCL tumors carrying control 3'UTR CXCL12 gene sequence (CXCL12+ PTCL).

- Primary Objective: ORR by IWC and/or mSWAT
- Target Population: PTCL relapsed or refractory to at least 1 prior systemic cytotoxic therapy.
- Study Design:

  Stages 1 and 2:
  - N=18 using a Simon 2-stage design. H0=10%, H1=30%

  Expansion Cohorts
  - AITL (N = 12). Bayesian design with informative prior. With this sample size, if 4 or more responses were observed, the probability that the true response rate in AITL subjects is at least 30% is 82.6%.
  - CXCL12+ PTCL (N=12, currently enrolling). Bayesian design with informative prior. With this sample size, if 2 or more responses are observed, the probability that the true response rate in CXCL12+ subjects is 10% or higher is at least 87%.
  - Tipifarnib 300 mg twice daily (bid) on days 1 – 21 of 28-day treatment cycles.
- Clinical trial information: NCT02464228
- Ancillary studies: CXCL12/CXCR4 expression was investigated in tumor bank samples of PTCL patients treated with standard of care agents. Experiments were conducted in a CD1 mouse model to determine the effect of tipifarnib on CXCL12 production by bone marrow stroma.

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RESULTS

PATIENT DISPOSITION

Patients Treated	N (%)	39 (100)
AITL	n (%)	19 (49)
Non-AITL	n (%)	20 (51)
Prior Lines of Therapy	Median (Range)	3 (1-7)
Total Discontinuations	n (%)	32 (82)
Progressive Disease	n (%)	24 (62)
Adverse Event	n (%)	5 (13)
Symptomatic Deterioration	n (%)	1 (3)
Withdrawal of Consent	n (%)	1 (3)
Transplant	n (%)	1 (3)

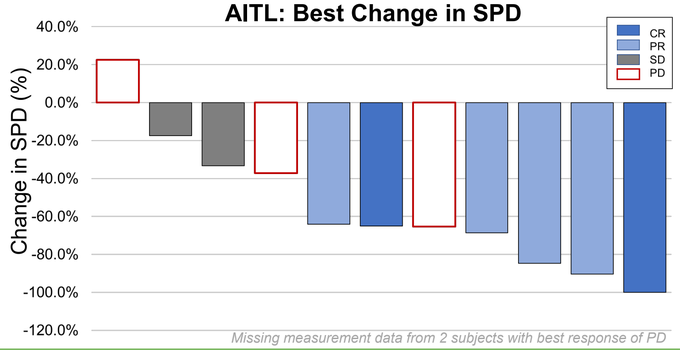
Results based on preliminary data as of 21 November 2018.

TIPIFARNIB ACHIEVES PROOF OF CONCEPT IN AITL

AITL: Overall Best Response

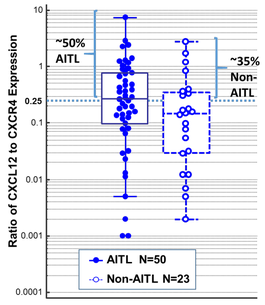
	AITL Cohort		All AITL	
	PP	mITT	PP	mITT
Total Treated	N = 10	N = 16	N = 13	N = 19
Overall Best Response				
CR	2	2	2	2
PR	2	2	4	4
SD	2	2	2	2
PD	4	4	5	5
NE	--	6 (2 pending)	--	6 (2 pending)
ORR (CR+PR)	**40%**	**25%**	**46%**	**32%**
Clinical Benefit (CR+PR+SD)	**60%**	**38%**	**62%**	**42%**

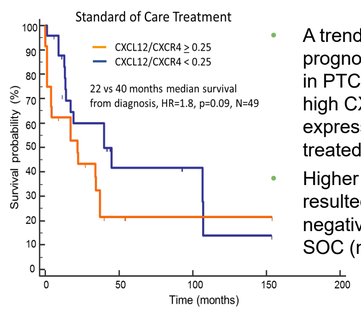
AITL: Best Change in SPD



Missing measurement data from 2 subjects with best response of PD

HIGH CXCL12 DEFINES POOR PROGNOSIS WITH STANDARD OF CARE THERAPY





- A trend for worse prognosis was observed in PTCL patients with high CXCL12/CXCR4 expression ratio when treated with SOC therapy
- Higher levels of CXCL12 resulted in significant negative prognosis for SOC (not shown)

SAFETY & TOLERABILITY

Treatment Related AEs (all grades) in ≥ 20% of Pts

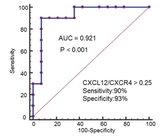
Cohort	PTCL NOS^ (N=15)	AITL* (N=17)	CXCL12+* (N=4)	ALCL^ (N=1)	Total (N=37)
Neutropenia	13 (86.7)	7 (41.2)	1 (25.0)	0	21 (56.8)
Thrombocytopenia	12 (80.0)	9 (52.9)	0	0	21 (56.8)
Anaemia	12 (80.0)	6 (35.3)	0	0	18 (48.6)
Diarrhoea	8 (53.3)	7 (41.2)	2 (50.0)	1 (100)	18 (48.6)
Nausea	10 (66.7)	5 (29.4)	2 (50.0)	0	17 (45.9)
Decreased appetite	8 (53.3)	6 (35.3)	2 (50.0)	0	16 (43.2)
Pyrexia	5 (33.3)	6 (35.3)	3 (75.0)	0	14 (37.8)
Fatigue	4 (26.7)	8 (47.1)	1 (25.0)	0	13 (35.1)
Leukopenia	8 (53.3)	2 (11.8)	0	0	10 (27.0)
Hypokalaemia	5 (33.3)	4 (23.5)	1 (25.0)	0	10 (27.0)
Dyspnoea	6 (40.0)	3 (17.6)	0	1 (100)	10 (27.0)
Vomiting	5 (33.3)	2 (11.8)	2 (50.0)	0	9 (24.3)
Febrile neutropenia	6 (40.0)	3 (17.6)	0	0	9 (24.3)
Hyponatraemia	7 (46.7)	1 (5.9)	1 (25.0)	0	9 (24.3)

^ Tipifarnib administered at a starting dose of 900 mg bid on Days 1 – 7 and 15 – 21 of 28-day treatment cycles.
* Tipifarnib administered at a starting dose of 300 mg bid on Days 1 – 21 of 28-day treatment cycles

- Safety information was available for 37 pts. Toxicities were consistent with known safety profile of tipifarnib.
- Hematologic events were manageable with treatment interruption, dose reductions and/or transfusion support.
- The initial dose regimen in stages 1 and 2 of the study was 900 mg bid on an alternate week regimen. The regimen was amended to 300 mg bid on days 1-21 of a 28-day treatment cycle for the two expansion cohorts to seek to improve the tolerability profile.

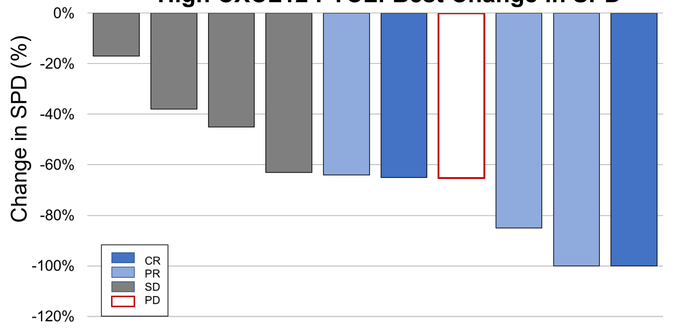
HIGH CXCL12 DEFINES GOOD PROGNOSIS WITH TIPIFARNIB THERAPY

HISTOL.	RESP.	CXCL12/CXCR4
AITL	PR	7.42
NOS	SD	0.85
AITL	CR	0.48
AITL	PD/NE	0.43
NOS	SD	0.40
NOS	PR	0.37
AITL	CR	0.36
AITL	PR	0.35
NOS	SD	0.30
AITL	SD	0.28
AITL	PD/NE	0.19
NOS	PD/NE	0.18
NOS	PD/NE	0.17
NOS	PD/NE	0.16
AITL	PR	0.15
ALCL	PD/NE	0.14
AITL	PD/NE	0.12
AITL	PD/NE	0.12
NOS	PD/NE	0.10
NOS	PD/NE	0.08
NOS	PD/NE	0.05
NOS	PD/NE	0.03
AITL	PD/NE	0.03
NOS	PD/NE	0.03



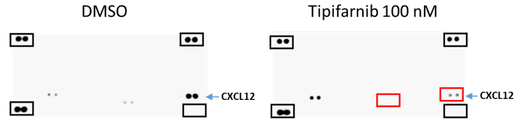
- **The High CXCL12/CXCR4 subset of PTCL pts experienced 50% ORR and 90% clinical benefit with tipifarnib after a median of 3 prior therapies**
- High CXCL12/CXCR4 expression ratio had 90% sensitivity and 93% specificity to identify PTCL pts likely to benefit from tipifarnib.

High CXCL12 PTCL: Best Change in SPD



Tipifarnib Downregulates CXCL12 production by Bone Marrow Stroma

Primary CD1 mouse BM cultures secrete abundant CXCL12 that is decreased by tipifarnib



CONCLUSIONS

- **CXCL12 is a stroma derived chemokine that promotes the progression of lymphoma and other tumors carrying the CXCR4 receptor.**
  - **High expression of CXCL12 was observed in ~40% of PTCL patients (50% of AITL tumors, 35% of Non-AITL tumors).**
  - **CXCL12 was found to be a negative prognostic factor for standard PTCL therapy.**
  - **Tipifarnib downregulates CXCL12 secretion from stroma cells.**
- **Encouraging activity was observed with tipifarnib in PTCL pts**
  - **Proof of concept achieved in AITL with a 46% ORR and 62% clinical benefit in AITL.**
  - **High CXCL12 expression identifies a particularly responsive subset within AITL and non-AITL, with a 50% ORR and 90% clinical benefit in pts with a median of three prior therapies.**
- **Tipifarnib was generally well-tolerated. Most common treatment-related AEs (grade ≥ 3) were hematology related, including neutropenia, thrombocytopenia, leukopenia, febrile neutropenia and anemia.**

References:
Gualberto et al. The CXCL12/CXCR4 Pathway As a Potential Target of Tipifarnib in Acute Myeloid Leukemia and Myelodysplastic Syndromes. ASH 2017
Ho et al.. Preliminary results from a Phase 2 proof of concept trial of tipifarnib in Squamous Cell Carcinomas (SCCs) with HRAS mutations. ESMO 2018
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Pass. FTase Inhibition Holds Promise for RAS Targeting and Beyond. Onclive 2018.