The CXCL12/CXCR4 Pathway as a Potential Target of Tipifarnib: Preliminary Results from an Open-Label, Phase II Study in Relapsed or Refractory Peripheral T-cell Lymphoma

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BACKGROUND

Tipifarnib:

- Potent and highly selective **inhibitor** of **Farnesyl Transferase (FT)**
- FT catalyzes post-translational attachment of farnesyl groups required for localization of signaling molecules to the inner cell membrane.

CXCL12

- Chemokine that is essential for T cell homing to lymphoid organs and the bone marrow, and for the maintenance of immune cell progenitors.
- CXCL12 has been postulated to signal in part through HRAS, a signaling protein that is uniquely dependent on farnesylation for activity.

METHODS

This is a Phase 2 study designed to investigate the antitumor activity of tipifarnib in patient (pts) with relapsed or refractory PTCL.

Primary Objective: ORR by IWC and/or mSWAT
Secondary Objectives: PFS, DOR, safety/tolerability
Exploratory Objectives: Biomarkers

Expansion Cohorts: AITL, CXCL12+ PTCL

- Based on observed antitumor activity and biomarker evaluation in stages 1 and 2, the study is being amended to include expansion cohorts in AITL (enrolling) and CXCL12+ PTCL (N = 12 each).
- Tipifarnib 300 mg twice daily (bid) on days 1 – 21 of 28-day treatment cycles.

Clinical trial information: NCT02464228

CONCLUSIONS

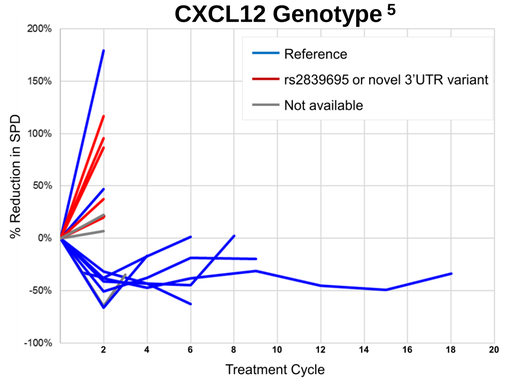
- **Encouraging activity of tipifarnib was observed in PTCL pts, particularly in those with tumors of AITL histology and high CXCL12 expression.**
- **Study is being amended to continue enrollment of pts with CXCL12+ PTCL. Enrollment in the AITL cohort is ongoing.**
- **Tipifarnib was generally well-tolerated. Most common treatment-related AEs (grade ≥ 3) were hematology related, including neutropenia, thrombocytopenia, leukopenia, anemia and febrile neutropenia.**

RESULTS

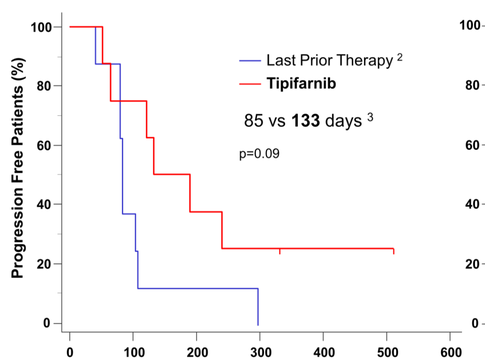
Clinical Benefit from Tipifarnib is Associated with CXCL12 Genotype

Results based on preliminary data as of 22 Nov 2017.

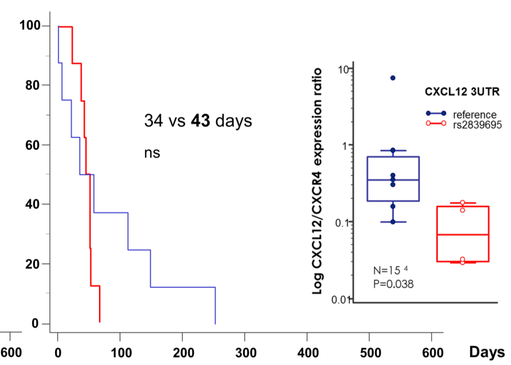
Percent Reduction in SPD Over Time by CXCL12 Genotype [5]



CXCL12 Reference 3UTR [1]



CXCL12 Variant 3UTR [3]

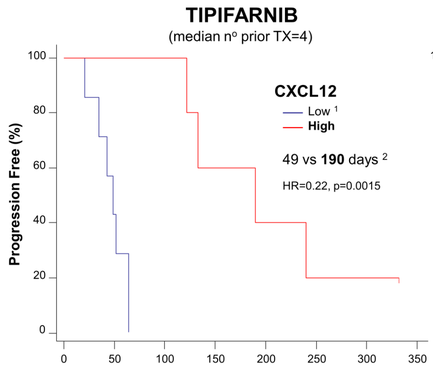


1. Eight subjects carried rs2839695; one subject presented a novel 3UTR variant, and 8 subjects carried reference 3UTR CXCL12 sequences
2. Last prior therapy: Chemotherapy (7), brentixumab (4), HDACi (2) lenalidomide (2), ruxolitinib (1)
3. Median overall PFS for tipifarnib (5th line) in subjects with NGS data was 53 days. Median overall PFS for these subjects on their last prior was 82 days
4. Low CXCL12 expression was observed in tumors samples carrying the CXCL12 rs2839695 3UTR variant
5. SPD data not available for 2 pts: 004-006, 004-007

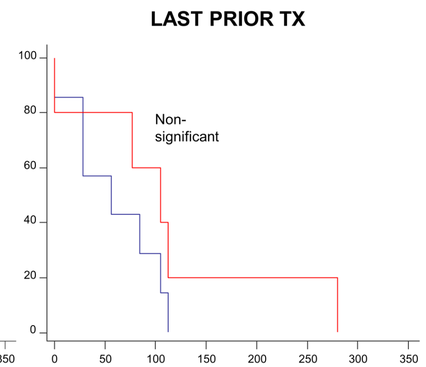
Clinical Benefit from Tipifarnib is Associated with CXCL12 Expression

CXCL12 expression was a specific biomarker of clinical benefit in patients receiving tipifarnib

TIPIFARNIB
(median nº prior TX=4)



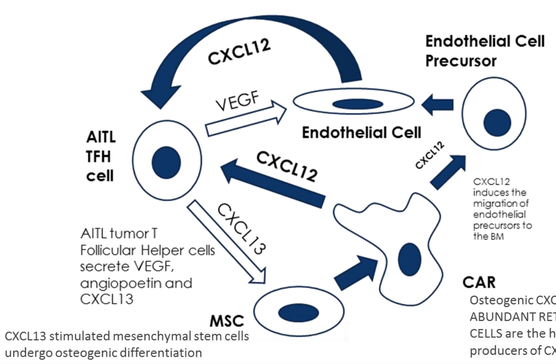
LAST PRIOR TX



1. Median overall PFS for tipifarnib (5th line) in subjects with NGS data was 53 days. Median PFS for the same subjects on their last prior was 84 days
2. Low CXCL12 expression was observed in tumors samples carrying the CXCL12 rs2839695 3UTR variant

RNA Seq Experiment#1

Pt ID	2002	2004	3002	4001	2001	4004
HIS	NOS	NOS	NOS	NOS	NOS	**AITL**
RESP	PD	PD	PD	SD	SD	**PR**
CXCL12	469	759	613	**2659**	**1160**	**3265**
CXCL13	4602	303	351	1729	1039	**25355**
VCAM1	3643	2328	1776	4111	1118	**7359**
PDGFRA	898	1538	1453	1038	440	1080
ANGPT1	0	21	188	84	0	28
TEK	495	634	791	734	138	691
GAPDH	17369	10574	9485	12101	6328	16189



RNA Seq Experiment#2

Pt ID	2005	2006	4005	4006	4007	6003	2007
HIS	NOS	NOS	NOS	NOS	NOS	NOS	**AITL**
RESP	PD	PD	PD	PD	PD	SD	**PR**
CXCL12	1570	325	834	1211	1081	**3728**	**14076**
CXCL13	**16876**	47	715	10	2088	424	1176
VCAM1	2874	1255	5746	546	5344	4785	**29134**
PDGFRA	1415	74	2037	2872	684	856	**6227**
ANGPT1	34	43	24	63	22	93	**769**
TEK	560	192	207	990	436	389	**4542**
GAPDH	45614	22595	15801	112381	17003	27244	10403

High CXCL12 expression may result from CXCL13-induced CXCL12 upregulation and angiogenesis

Patient Disposition

Total Treated	N (%)	19 (100)
AITL	n (%)	3 (16)
ALCL, ALK negative	n (%)	1 (5)
PTCL, NOS	n (%)	15 (79)
Prior Lines of Therapy	Median (Range)	4 (1 – 7)
Total Discontinuations	n (%)	17 (89)
Reasons for Discontinuation:		
Progressive Disease	n (%)	16 (94)
Withdrawal of Consent	n (%)	1 (6)

Safety & Tolerability

- Toxicities were consistent with the known safety profile of tipifarnib.
- Grade ≥ 3 drug-related TEAEs occurring in ≥ 10% of pts were hematology related: neutropenia (74%), thrombocytopenia (58%), leukopenia (47%), anemia and febrile neutropenia (32% each) and lymphopenia (16%).
- Myelosuppression was manageable with treatment interruption, dose reductions, growth factor or transfusion support.
- The dose regimen was amended to 300 mg bid on days 1-21 of 28 day treatment cycles due to the observed tolerability profile of the alternate week regimen tested in stages 1 and 2 of the study.

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