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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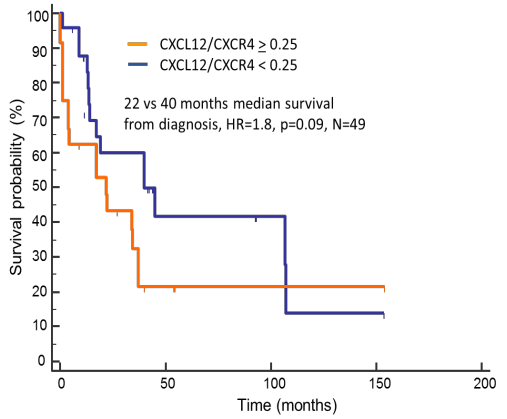
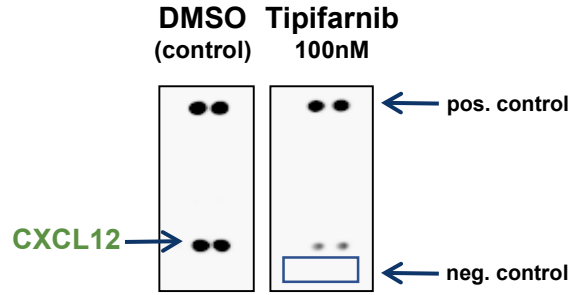
Tipifarnib is a CXCL12/CXCR4 Pathway Inhibitor

- **Key characteristics of CXCL12**
  - Expressed primarily by immune cells, endothelial cells and stromal fibroblasts that constitute the tumor microenvironment
  - CXCL12 and its receptors (CXCR4, CXCR7) are key factors linking cancer cells with the tumor microenvironment
- **High CXCL12 expression defines poor prognosis in PTCL**
  - 50% of AITL and 35% of PTCL-NOS have high CXCL12 expression
  - Trend for worse prognosis in AITL and PTCL-NOS patients with tumors with high CXCL12 expression[1]
- **Tipifarnib is a CXCL12/CXCR4 pathway inhibitor**
  - Tipifarnib downregulates CXCL12 secretion ex-vivo in stroma cultures
  - Expression of uniquely farnesylated proteins (RHOE and PRICKLE2) is strongly correlated with CXCL12 expression, suggesting potential CXCL12-related tipifarnib targets[2]
  - Resistance to tipifarnib potentially mediated by CXCR2 and its ligands (CXCL1, CXCL5, CXCL8) in myeloid indications[3]



Trend for poor prognosis with high CXCL12 expression (adjusted to CXCR4) in AITL and PTCL NOS pts



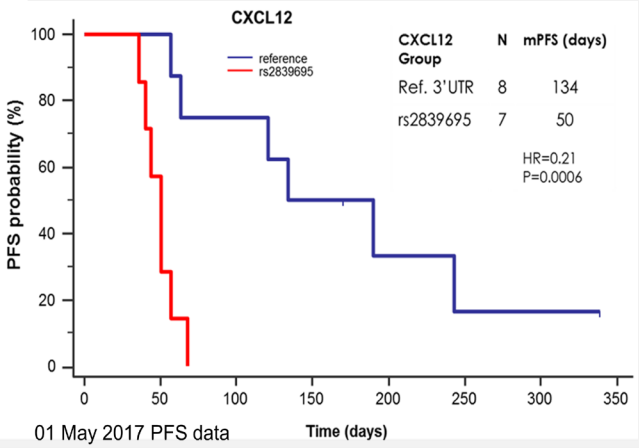
Tipifarnib downregulates the secretion of CXCL12 ex-vivo in CD1 mouse bone marrow cultures

[1] Witzig 2018 *Blood* 132:2937 | [2] Gualberto EHA 2019 #PS1002 | [3] Gualberto *Blood* 2017 130:3957

Study Design[1]

Original Protocol: Stages 1 and 2

- R/R PTCL, ≥ 1 prior systemic therapy, measurable disease by Lugano Classification and/or mSWAT, ECOG 0-2
- Tipifarnib 600 - 900 mg orally (po) twice daily (bid) on days 1-7 and days 15-21 every 28 days
- Simon 2-stage design (11+7 pts)
- Hypothesis: 10% (H0) vs 30% (H1) ORR, a=0.05, 80% power
- Results[2]:
  - Primary objective not met. Only 3 of 4 responses needed observed.
  - Antitumor activity (PR, SD) observed in AITL and PTCL-NOS pts with high levels of tumor CXCL12 gene expression in retrospective analyses.
  - High CXCL12 expression observed tumors with wild type CXCL12 3'UTR



The rs2839695 A>G Variant in the 3'UTR CXCL12 observed in patients with PD

rs2839695 A>G lowers CXCL12 expression, is present in stromal cells and is detectable in buccal swabs

AITL Cohort (N=12)

- R/R AITL, ≥ 1 prior systemic therapy, measurable disease, ECOG 0-2
- Tipifarnib 300 mg po bid on days 1-21 every 28 days
- Hypothesis: If ≥ 4 responses observed, 82.6% probability that the true response rate is at least 30%.

Wild type (wt) CXCL12 3'UTR Cohort (N=12)

- R/R PTCL, ≥ 1 prior systemic therapy, measurable disease, ECOG 0-2; AITL pts could be enrolled once the AITL cohort enrollment was complete.
- wt CXCL12 3'UTR defined by PCR of the rs2839695 locus in buccal swabs
- Tipifarnib 300 mg po bid on days 1-21 every 28 days
- Hypothesis: If ≥ 2 responses observed, 89% probability that the true response rate is at least 10%.

[1] NCT02464228, KO-TIP-002 | [2] Witzig 2017 *Hematol Oncol* 35(S2): 251–2

Patient Demographics

	Stage 1/2	AITL Cohort	wt CXCL12 3'UTR Cohort [1]	Total
Total Patients Treated, n (%)	19 (100) [2]	16 (100)	15 (100)	**50 (100)**
Total Evaluable for Efficacy [3], n (%)	18 (94.7) [2]	11 (68.8)	12 (80.0)	**41 (82.0)**
Histology				
AITL, n (%)	3 (15.8)	16 (100)	4 (26.7)	**23 (46.0)**
PTCL-NOS, n (%)	14 (73.7)	0	11 (73.3)	**25 (50.0)**
Other, n (%)	2 (10.5)	0	0	**2 (4.0)**
Age, yrs				
Median	66.7	66.9	65.2	**66.7**
Min, Max	31, 87	45, 87	38, 80	**31, 87**
Male, n (%)	15 (78.9)	11 (68.8)	9 (60.0)	**35 (70.0)**
Female, n (%)	4 (21.1)	5 (31.2)	6 (40.0)	**15 (30.0)**
Number of Prior Anti-Cancer Regimens				
Median	4	3	3	**3**
Min, Max	1, 7	1, 7	1, 8	**1, 8**
Prior Auto BMT [4], n (%)	6 (31.6)	7 (43.8)	6 (40.0)	**19 (38.0)**

[1] Subjects have wild type CXCL12 rs2839695 A/A genotype determined by PCR of buccal swabs. Subjects with rs2839695 A/G and G/G were excluded.
[2] One subject was enrolled with a non-eligible histology and replaced
[3] To be evaluable for efficacy, eligible pt must have received at least 1 dose of tipifarnib and have at least 1 post baseline tumor response assessment
[4] One pt with unknown transplant type

Preliminary data as of 24 May 2019

Proof of Concept for Tipifarnib in wt CXCL12 3'UTR PTCL

	wt CXCL12 3'UTR Cohort: All pts		wt CXCL12 3'UTR Cohort: AITL pts		wt CXCL12 3'UTR Cohort: PTCL-NOS pts	
Total treated	15		4		11	
Total efficacy evaluable	12		3		9	
Overall Best Response						
Complete Response (CR)	3		2		1	
Partial Response (PR)	2		-		2	
Stable Disease (SD)	6		-		6	
Progressive Disease (PD)	1		1		-	
Not efficacy evaluable (NE)	3		1		2	
	PPS[1]	mITT	PPS[1]	mITT	PPS[1]	mITT
Overall Response Rate[1] (CR + PR)	**41.7%**	**33.3%**	**66.7%**	**50%**	**33.3%**	**27.3%**
95% CI	18.1 – 70.6	14.2 - 60.6	13.5 - 98.3	9.8 - 90.2	9.8 - 68.4	7.9 - 59.9
Clinical Benefit Rate[1] (CR + PR + SD)	**91.7%**	**73.3%**	**66.7%**	**50%**	**100%**	**81.8%**
95% CI	63.4 - 99.6	46.5 - 90.3	13.5 - 98.3	9.8 - 90.2	68.4 - 100.0	50.0 - 96.7

[1] Per protocol set – prespecified primary analysis population includes all pts who received at least 1 dose of tipifarnib and have 1 post-baseline tumor measurement

Preliminary data as of 24 May 2019

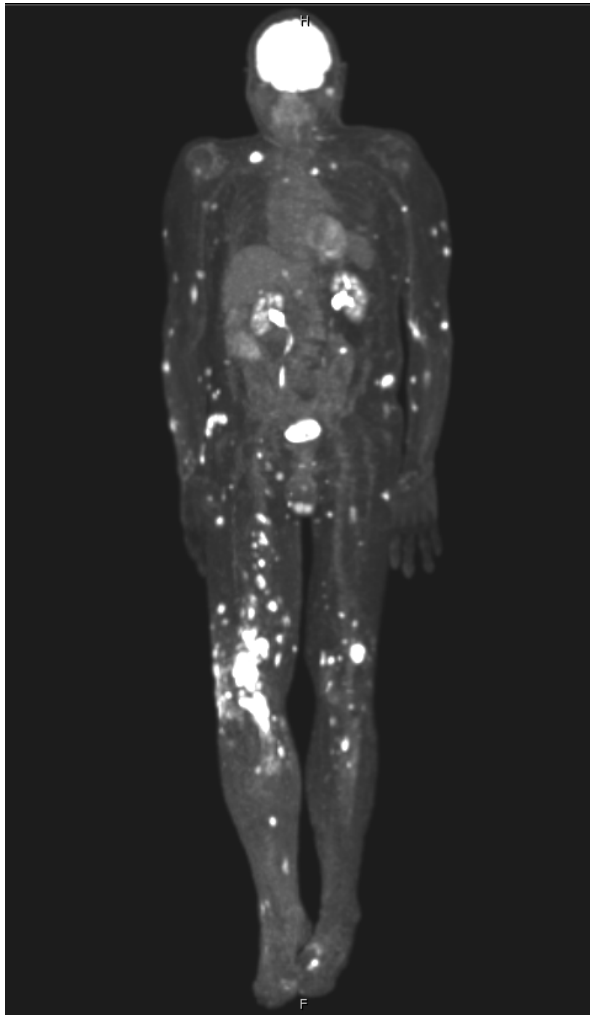
Enrichment by wt CXCL12 3'UTR PTCL-NOS

	All PTCL-NOS wt CXCL12 3'UTR[1]		All PTCL-NOS Variant CXCL12 3'UTR[2]
Total treated	17		6
Total efficacy evaluable	15		6
Overall Best Response			
Complete Response (CR)	1		-
Partial Response (PR)	2		-
Stable Disease (SD)	10		-
Progressive Disease (PD)	2		6
Not efficacy evaluable (NE)	2		-
	PPS[3]	mITT	PPS/mITT
Overall Response Rate (CR + PR)	**20%**	**17.6%**	**0%**
95% CI	5.7 - 46.5	5.0 - 41.7	0 - 40.6
Clinical Benefit Rate (CR + PR + SD)	**86.7%**	**76.5%**	**0%**
95% CI	60.6 - 97.6	51.1 - 91.5	0 - 40.6

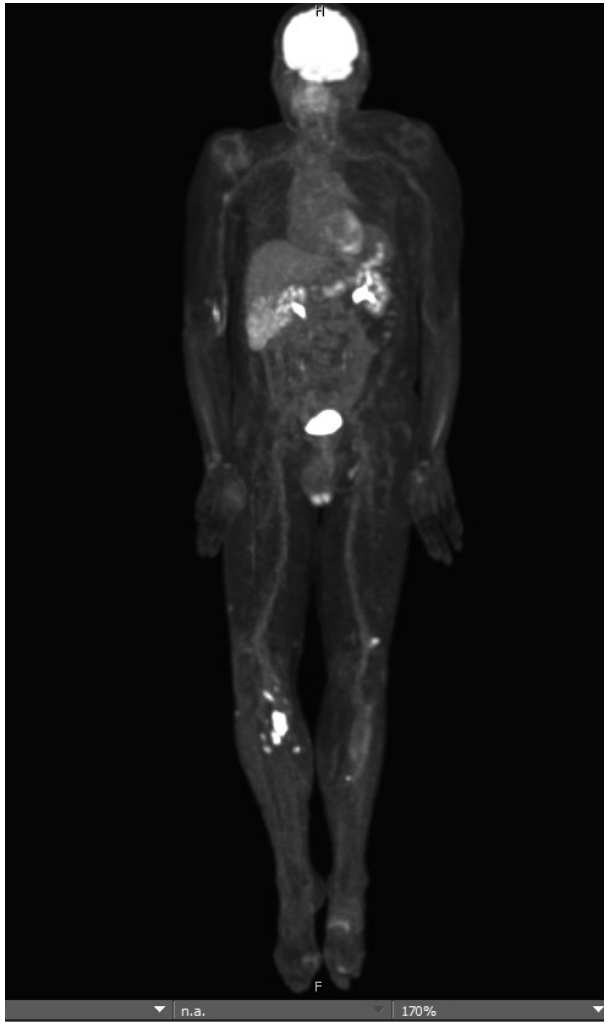
[1] All PTCL-NOS wt CXCL12 3'UTR includes all PTCL-NOS pts with CXCL12 rs2839695 A/A genotype enrolled in all portions of the trial.
[2] Includes PTCL-NOS pts with CXCL12 rs2839695 A/G or G/G genotype (enrolled in the original protocol stages 1 and 2)
[3] Per protocol set – prespecified primary analysis population includes all pts who received at least 1 dose of tipifarnib and have 1 post-baseline tumor measurement

Preliminary data as of 24 May 2019

Tumor Reduction in PTCL-NOS, wt CXCL12 3'UTR



Baseline



End of Cycle 2

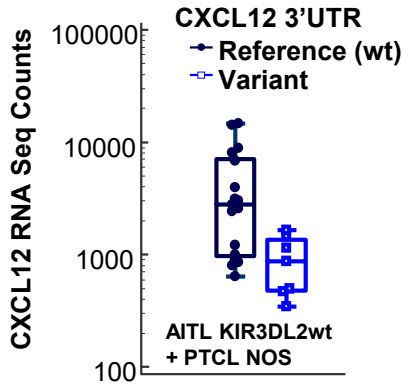
- 77 yo male with PTCL-NOS Stage IV
- CHOP x 5 with initial response then progression in skin
- At baseline visit had multiple skin nodules biopsy proven relapsed PTCL
- After two cycles of tipifarnib patient had near CR

Drivers of Tipifarnib's Activity in wt CXCL12 3'UTR NOS

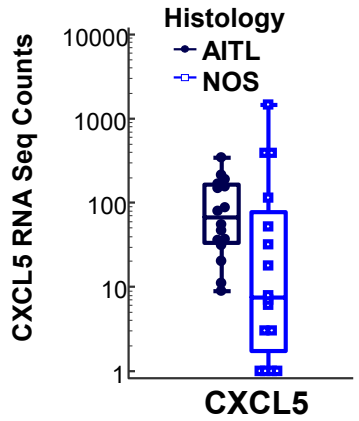
High CXCL12 in subjects with wt CXCL12 3'UTR, Overall low CXCL5 expression in NOS

Genetics

High CXCL12 in subjects with wt CXCL12 3'UTR



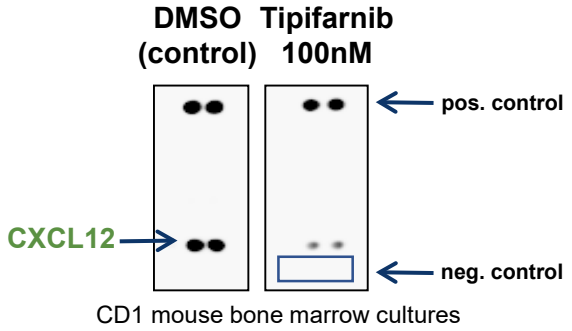
Low CXCL5 expression in NOS



Low CXCL5 mediated resistance

Mechanism of Action

Tipifarnib downregulates CXCL12 secretion



CD1 mouse bone marrow cultures

Activity

	wt CXCL12 3'UTR
N, AITL (KIR3DL2wt) + NOS	17
Overall Best Response	
Complete Response (CR)	1
Partial Response (PR)	3
Stable Disease (SD)	6
Progressive Disease (PD)	-
Not evaluable (NE)	-
Overall Response Rate	**23.5%**
Clinical Benefit Rate	**58.8%**

N= 32 AITL/NOS cases with response, NGS and RNA Seq data

Proof of Concept for Tipifarnib in AITL

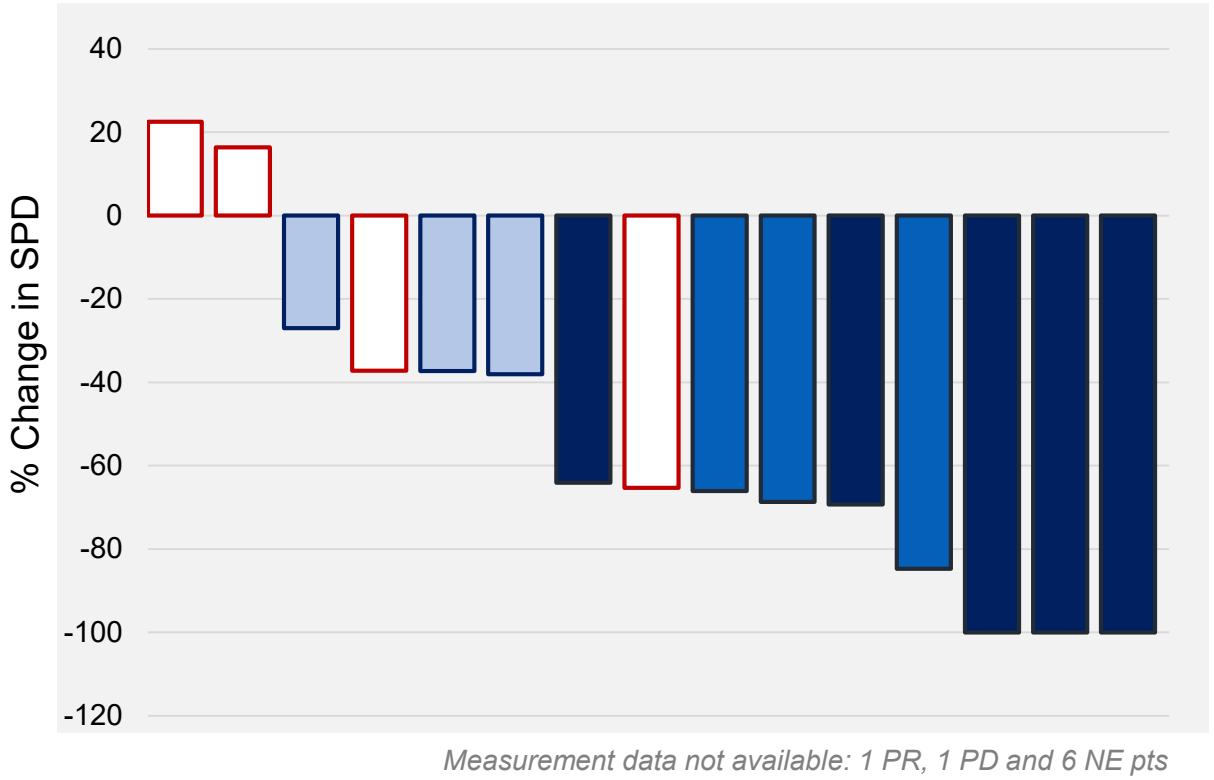
	AITL Cohort		All AITL [1]	
Total treated	16		23	
Total efficacy evaluable	11		17	
Overall Best Response				
Complete Response (CR)	3		5	
Partial Response (PR)	2		4	
Stable Disease (SD)	3		3	
Progressive Disease (PD)	3		5	
Not efficacy evaluable (NE)	5		6	
	PPS[2]	mITT	PPS[2]	mITT
Overall Response Rate (CR + PR)	**45.4%**	**31.3%**	**52.9%**	**39.1%**
95% CI	20.0 - 74.4	13.2 - 56.6	28.2 - 74.7	20.7 - 61.3
Clinical Benefit Rate (CR + PR + SD)	**72.7%**	**50.0%**	**70.6%**	**52.2%**
95% CI	40.1 - 92.1	27.2 - 72.8	45.6 - 87.6	32.0 - 72.6

[1] All AITL includes all AITL pts enrolled in all portions of the trial: original protocol (stages 1 and 2), AITL cohort and wt CXCL12 3'UTR cohort.
[2] Per protocol set – prespecified primary analysis population includes all pts who received at least 1 dose of tipifarnib and have 1 post-baseline tumor measurement.

Preliminary data as of 24 May 2019

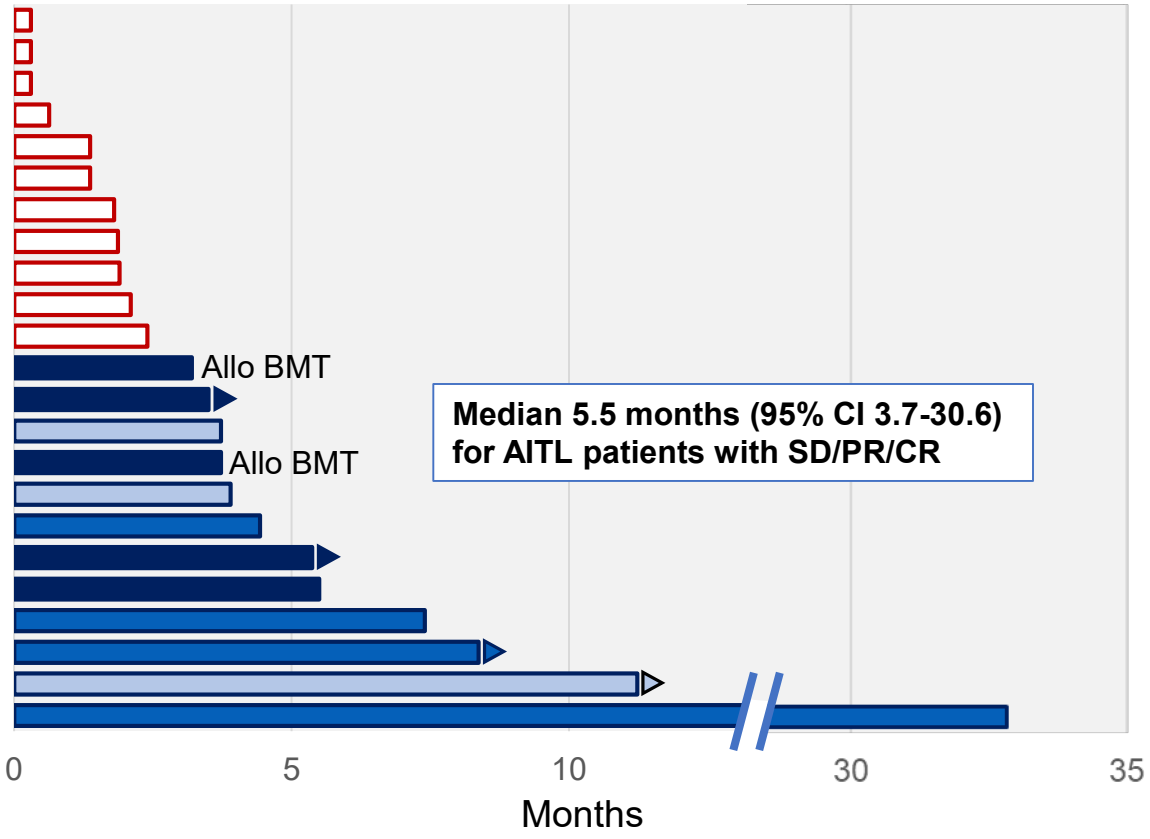
AITL: Tipifarnib treatment resulted in durable clinical responses and enabled subsequent transplant in patients achieving a CR

Maximum Change in Tumor Burden



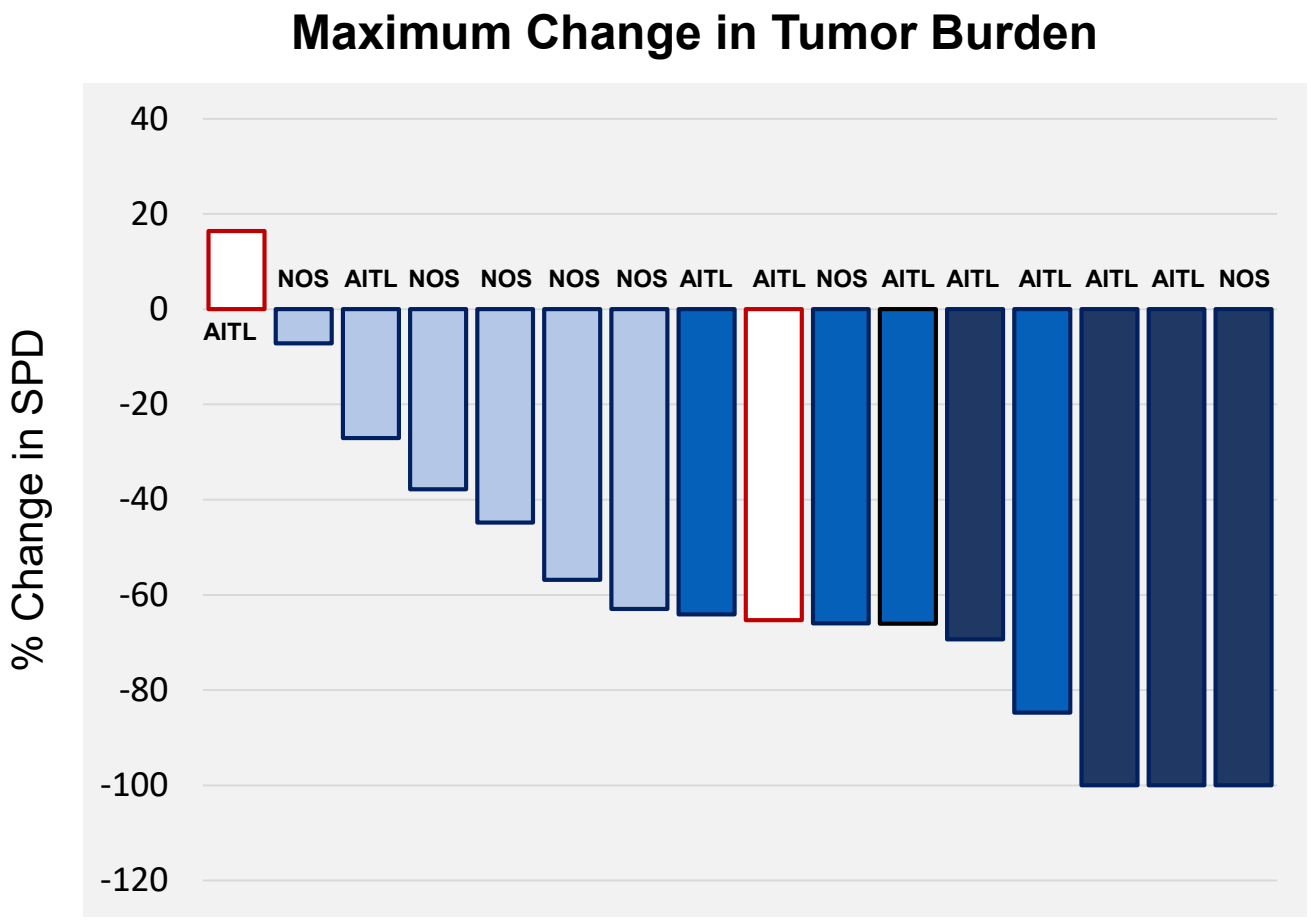
Measurement data not available: 1 PR, 1 PD and 6 NE pts

Time on Treatment



Preliminary data as of 24 May 2019

Tipifarnib is Active in High CXCL12 Expressing AITL and PTCL NOS Tumors



Cases with available RNA Seq data and CXCL12/CXCR4 > 0.2. 1 PD case missing tumor measurements

sample	HISTOL	RESP	CXCL12/CXCR4
6	AITL	PR	7.42
28	AITL	CR	2.4
34	AITL	PD/NE	
36	NOS	SD	1.3
17	NOS	SD	0.85
32	AITL	PD/NE	
37	NOS	SD	0.6
1	AITL	CR	0.48
30	AITL	PR	0.4
7	AITL	PD/NE	
18	NOS	SD	0.40
12	NOS	CR	0.37
2	AITL	CR	0.36
3	AITL	PR	0.35
16	NOS	SD	0.30
31	NOS	PR	0.28
5	AITL	SD	0.28
8	AITL	PD/NE	0.19
23	NOS	PD/NE	0.18
40	NOS	PD/NE	0.17
19	NOS	PD/NE	0.16
4	AITL	PR	
26	ALCL	PD/NE	0.14
41	NOS	SD	0.1
10	AITL	PD/NE	0.12
11	AITL	PD/NE	0.12
20	NOS	PD/NE	0.10
25	NOS	PD/NE	0.08
33	AITL	SD	0.1
21	NOS	PD/NE	0.05
29	AITL	CR	
13	NOS	PD/NE	0.03
9	AITL	PD/NE	0.03
24	NOS	PD/NE	0.03

Tipifarnib targets CXCL12 and is active in tumors with high CXCL12 expression[1].

However, high CXCL12 could not explain all the activity/resistance to tipifarnib in AITL.

Molecular screenings were conducted to identify other drivers of the activity of tipifarnib in AITL.

[1] N = 34 tumors with available CXCL12 expression data.

Preliminary data as of 24 May 2019

High Activity of Tipifarnib in AITL with KIR3DL2 mutations

- CXCL12 and CXCL5 drive, respectively, sensitivity and resistance to tipifarnib.
- AITL expresses high levels of CXCL12 and is sensitive to tipifarnib.
- AITL also expresses CXCL5; however, ~50% of AITL carry mutations of KIR3DL2, express low levels of CXCL5 and are highly sensitive to tipifarnib (50% CR rate).
- High Allele Frequency of KIR3DL2 mutation predicted complete response to tipifarnib treatment (ROC AUC=0.94, p<0.0001).
- AITL patients carrying KIR3DL2 mutations experienced a better outcome with tipifarnib treatment than with prior SOC treatment.

Best Response to Tipifarnib (N=16 AITL with sequenced tumors)

	KIR3DL2 Mutant	KIR3DL2 Wild Type
N	8	8
Overall Best Response		
Complete Response (CR)	4	-
Partial Response (PR)	2	2
Stable Disease (SD)	2	-
Progressive Disease (PD)	-	6
Not evaluable (NE)	-	-
Overall Response Rate (CR + PR)	**75%**	**25%**
95% CI	35.9 - 95.4	4.6 - 64.1
Clinical Benefit Rate (CR + PR + SD)	**100%**	**25%**
95% CI	64.1 - 100.0	4.6 - 64.1

KIR data analyses to be presented at 15-ICML: Gualberto et. al. Abstract 156-P

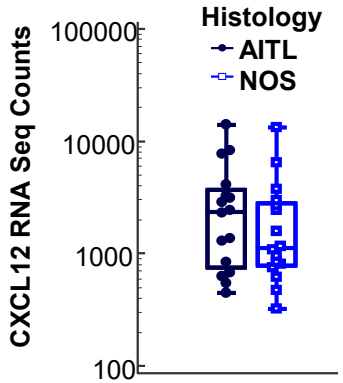
Preliminary data as of 24 May 2019

Drivers of Tipifarnib's Activity in AITL

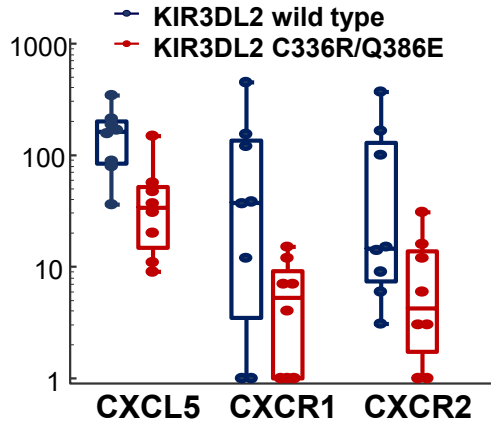
Overall high CXCL12 expression in AITL, Low CXCL5 expression in KIR3DL2 mutant AITL

Genetics

High CXCL12 expression in AITL histology

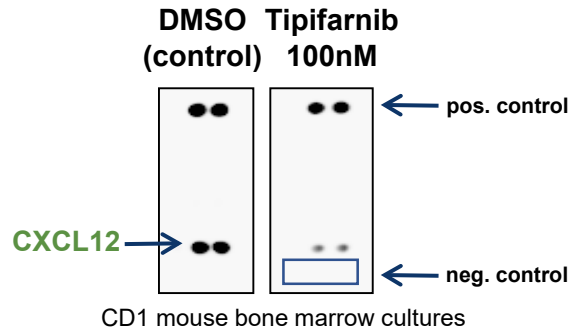


Low CXCL5 expression in KIR3DL2 mutant AITL

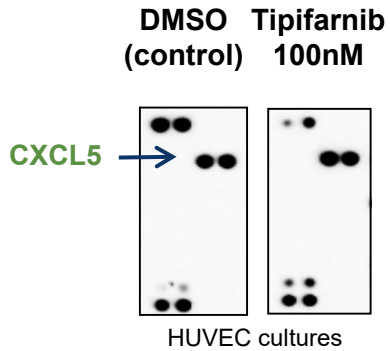


Mechanism of Action

Tipifarnib downregulates CXCL12 secretion



Tipifarnib does not inhibit CXCL5 secretion



Activity

	AITL KIR3DL2 Mutant
N	8
Overall Best Response	
Complete Response (CR)	4
Partial Response (PR)	2
Stable Disease (SD)	2
Progressive Disease (PD)	-
Not evaluable (NE)	-
Overall Response Rate	**75%**
Clinical Benefit Rate	**100%**

N= 32 AITL/NOS cases with response, NGS and RNA Seq data

Safety and tolerability of tipifarnib in PTCL

- All patients (N = 48)[1] had at least one treatment-emergent adverse event (TEAE); 42 (88%) had at least 1 study drug-related TEAE and 13 (27%) had at least 1 study drug-related SAE. One study drug related death (lung infection) has been reported.
- TEAEs were consistent with the known safety profile of tipifarnib. Most frequently observed TEAEs (all grades, ≥ 10% pts) were hematological-related events (thrombocytopenia, neutropenia, anemia and leukopenia), gastrointestinal disturbances (diarrhea and nausea), fatigue, decreased appetite and rash (maculo-popular).
- Improved tolerability (decreased frequency and severity of TEAEs) was observed with 300 mg bid administered days 1-21 every 28-days. 28% of pts on this schedule were dose reduced to 200 mg bid.

Grade 3 or Higher Study Drug Related TEAEs (≥ 10% pts)

	300 mg bid days 1-21 (n = 30) [1]	600 – 900 mg bid days 1-7 and 15-21 (n = 18)
Patients With at Least One Gr 3 or Higher Related TEAE, n (%)	15 (50.0)	16 (88.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS, n (%)	11 (36.7)	15 (83.3)
Thrombocytopenia	6 (20.0)	10 (55.6)
Neutropenia	5 (16.7)	14 (77.8)
Leukopenia	3 (10.0)	9 (50.0)
Anaemia	2 (6.7)	7 (38.9)
Febrile neutropenia	2 (6.7)	7 (38.9)
Lymphopenia	1 (3.3)	3 (16.7)

[1] Two treated pts are excluded since no safety data had been entered into the clinical database as of 24 May 2019.

Preliminary data as of 24 May 2019

Conclusions

- The AITL and wt CXCL12 3'UTR cohorts met pre-specified statistical hypotheses supporting proof-of-concept for tipifarnib in PTCL.
- Tipifarnib is active in AITL pts and in PTCL-NOS pts with wt CXCL12 3'UTR
  - AITL: 53% ORR (all subjects, PPS)
  - PTCL-NOS with wt CXCL12 3'UTR: 20% ORR (all subjects, PPS).
- KIR3DL2 and CXCL12 genotype provide robust tools for the selection/stratification of patients:
  - CXCL12 genotype may enrich for CXCL12 expression and tipifarnib activity, particularly in PTCL-NOS (86.7% Clinical Benefit Rate for PTCL-NOS patients with wt CXCL12 3'UTR).
  - KIR3DL2 C336R/Q383E mutations may enrich for low CXCL5 expression and anti-tumor activity in AITL (75% ORR, 50% CR rate).
  - Approximately 50% of AITL carry KIR3DL2 mutations and 70% of PTCL carry reference (wild type) CXCL12 3'UTR rs2839695 sequences.
- TEAEs were consistent with the known safety profile of tipifarnib.
  - Treatment with tipifarnib 300 mg bid days 1-21 every 28-days was generally well tolerated. The majority of Grade ≥ 3 TEAEs were hematological events managed with best supportive care.
- These results suggest that further evaluation of tipifarnib in biomarker defined subsets of PTCL and CTCL would be of interest.

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- Patients, their families and caregivers
- Study Investigators and their study teams
- Kura Oncology