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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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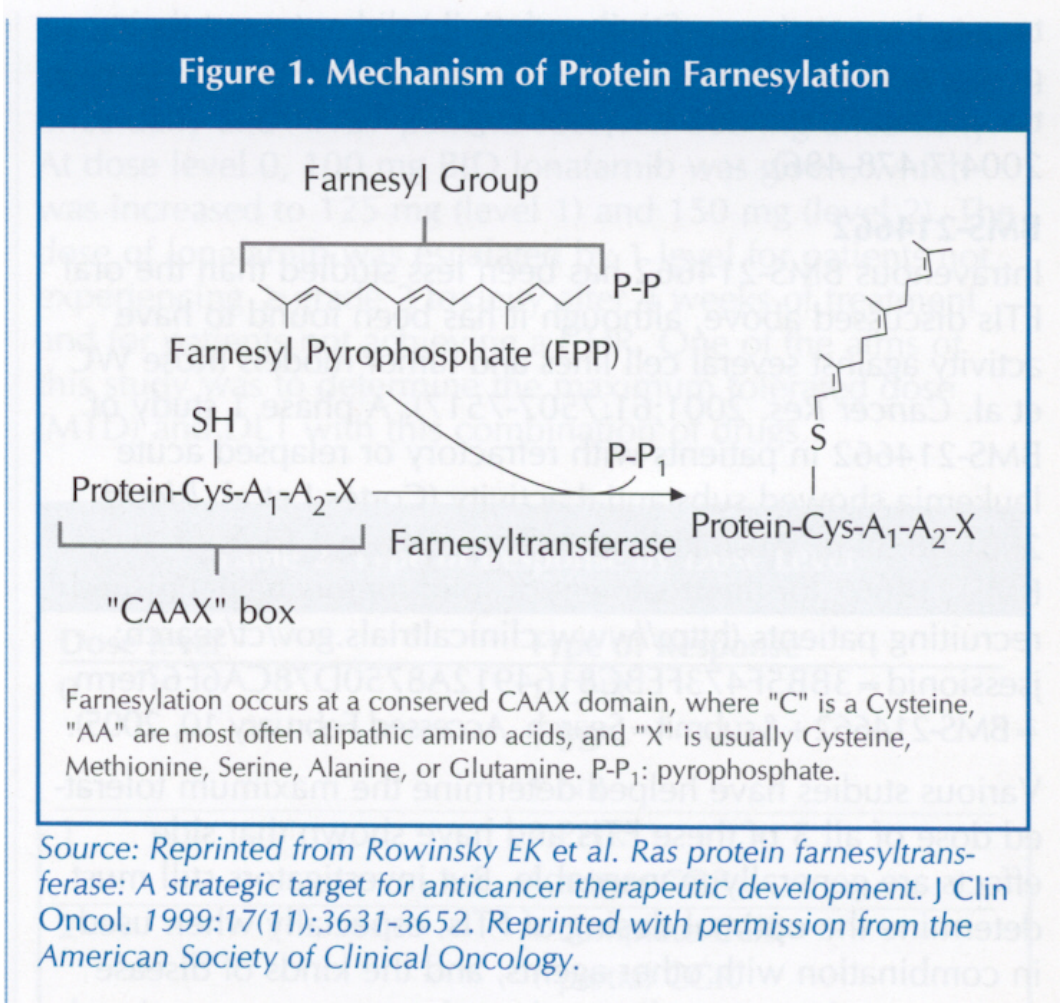
Disclosures

- Clinical Trials Support to conduct the trials: Acerta, Celgene, Kura Oncology, Spectrum
- Advisory Boards (personally uncompensated): Incyte, Seattle Genetics, Abbvie, Morphosys, Spectrum, Celgene
- Advisory Boards (personally compensated): Immune Design, Karyopharm, Epizyme (April 2019)

Tipifarnib is a Farnesyltransferase (FT) Inhibitor

- FT adds a 15 carbon farnesyl group to proteins with CAAX motif
  - C = cysteine; A = aliphatic a.a. X= determines which enzyme does the prenylation
- Tipifarnib is an oral FTI that has been tested in >5000 unselected patients with a variety of solid and blood cancers
- Studies in lymphoma 2004-2008
  - Blood. 2011;118(18): 4872-4881
  - Blood. 2011; 118(18):4882-4889



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Cytotoxicity of farnesyltransferase inhibitors in lymphoid cells mediated by MAPK pathway inhibition and Bim up-regulation

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Multi-institutional phase 2 study of the farnesyltransferase inhibitor tipifarnib (R115777) in patients with relapsed and refractory lymphomas

Thomas E. Witzig,[1] Hui Tang,[2] Ivana N. M. Micallef,[1] Stephen M. Ansell,[1] Brian K. Link,[3] David J. Inwards,[1] Luis F. Porrata,[1] Patrick B. Johnston,[1] Joseph P. Colgan,[1] Svetomir N. Markovic,[1] Grzegorz S. Nowakowski,[1] Carrie A. Thompson,[1] Cristine Allmer,[2] Matthew J. Maurer,[2] Mamta Gupta,[1] George Weiner,[3] Ray Hohl,[3] Paul J. Kurtin,[4] Husheng Ding,[5] David Loegering,[5] Paula Schneider,[5] Kevin Peterson,[5] Thomas M. Habermann,[1] and Scott H. Kaufmann[1,5]

ORR in all 93 patients = 20%

NCT00082888; LS038B Iowa/Mayo SPORE trial

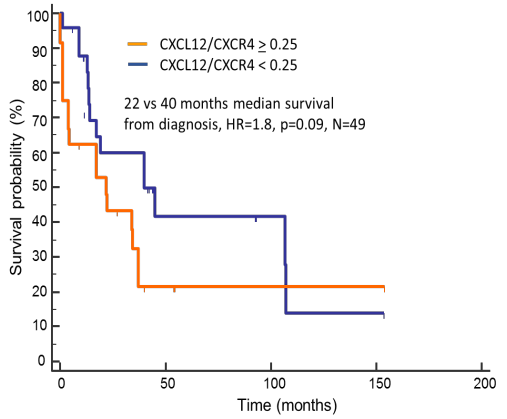
Goals of this Presentation

- To review preliminary data from a new ongoing phase 2 study (KO-TIP-002) of single-agent tipifarnib
  - Drug in-licensed to Kura Oncology from Janssen/Johnson & Johnson
  - Single-agent tipifarnib at two different schedules:
    - 300 mg po bid days 1-21 q28 days
    - 600 - 900 mg po bid days 1-7 and days 15-21 q28 days

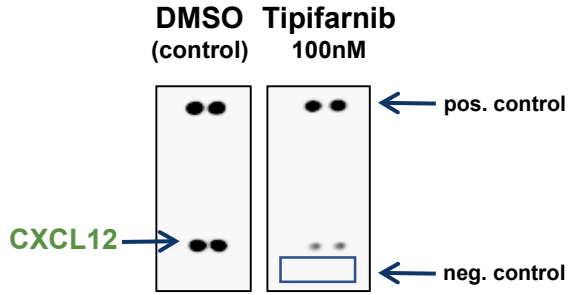
- Demonstrate how biomarkers learned from unselected pts can be used prospectively to select patients and enrich the ORR.
  - CXCL12 and its receptor CXCR4
  - KIR3DL2 mutations

Tipifarnib is a CXCL12/CXCR4 Pathway Inhibitor

- **Key characteristics of CXCL12**
  - 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 ligand CXCL5[3]**



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



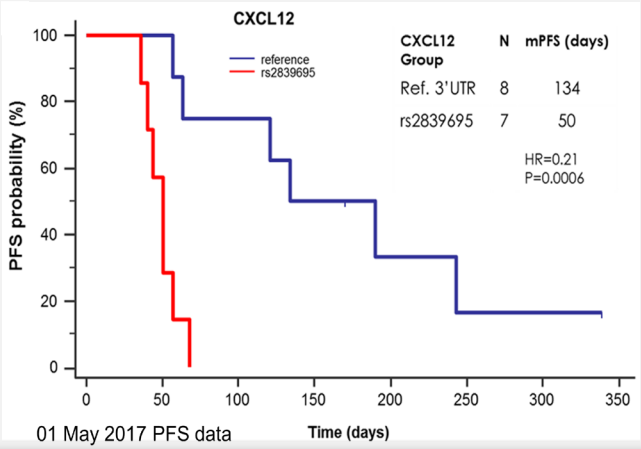
Tipifarnib downregulates the secretion of CXCL12 ex-vivo in CD1 mouse bone marrow cultures

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

Study Design of KO-TIP-002[1]

Protocol Stages 1 and 2

- ***Unselected R/R PTCL, including AITL and PTCL-NOS***
- Tipifarnib 600 - 900 mg orally (po) twice daily (bid) on days 1-7 and days 15-21 every 28 days
- **Results[2]:** Primary objective not met. Only 3 of the 4 responses needed were observed in first unselected 19 patients.
- **Biomarker Analysis:**
  - 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 correlated with wild type CXCL12 3'UTR gene sequences.



The rs2839695 A>G Variant in the 3'UTR CXCL12 observed in pts that progressed.

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

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

- R/R PTCL, ≥ 1 prior 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%.

AITL Cohort (N=12)

- R/R AITL, ≥ 1 prior 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%.

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

Patient Demographics for Ongoing KO-TIP-002

	wt CXCL12 3'UTR Cohort [1]	AITL Cohort
Total Patients Treated, n (%)	15 (100)	16 (100)
Total Evaluable for Efficacy [2], n (%)	12 (80.0)	11 (68.8)
Histology		
AITL, n (%)	4 (26.7)	16 (100)
PTCL-NOS, n (%)	11 (73.3)	0
Other, n (%)	0	0
Age, yrs		
Median	65.2	66.9
Min, Max	38, 80	45, 87
Male, n (%)	9 (60.0)	11 (68.8)
Female, n (%)	6 (40.0)	5 (31.2)
Number of Prior Anti-Cancer Regimens		
Median	3	3
Min, Max	1, 8	1, 7
Prior Auto BMT [3], n (%)	6 (40.0)	7 (43.8)

[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] 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
[3] One pt with unknown transplant type

Preliminary data as of 24 May 2019

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

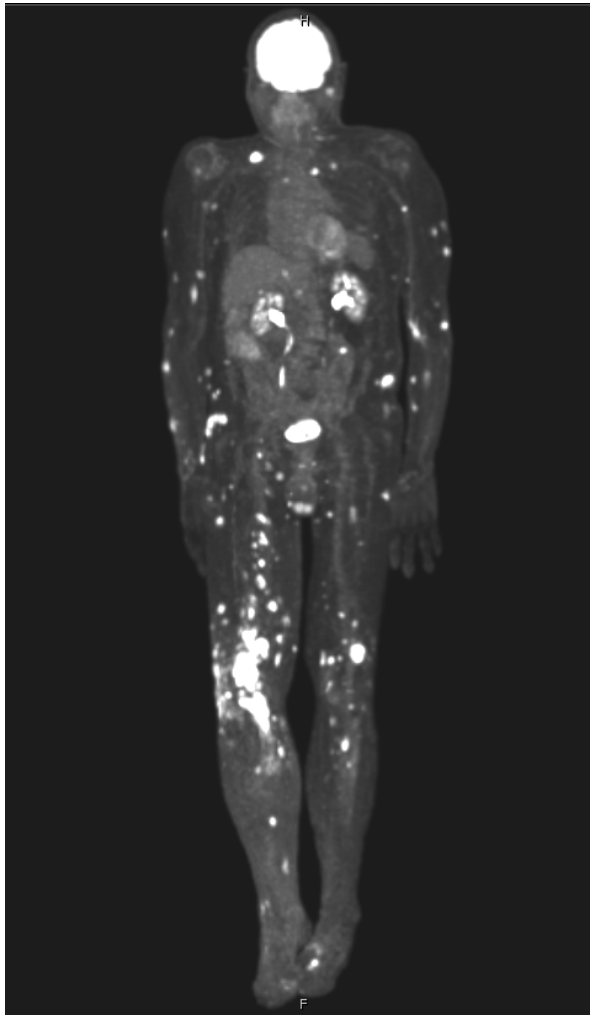
	wt CXCL12 3'UTR Cohort: All patients		wt CXCL12 3'UTR Cohort: PTCL-NOS		Variant CXCL12 3'UTR PTCL-NOS enrolled in S1/2
Total treated	15		11		6
Total efficacy evaluable	12		9		6
Overall Best Response					
Complete Response (CR)	3		1		-
Partial Response (PR)	2		2		-
Stable Disease (SD)	6		6		-
Progressive Disease (PD)	1		-		6
Not efficacy evaluable (NE)	3		2		-
	PPS[1]	mITT	PPS[1]	mITT	PPS/mITT
Overall Response Rate (CR + PR)	**41.7%**	**33.3%**	**33.3%**	**27.3%**	**0%**
95% CI	18.1 – 70.6	14.2 - 60.6	9.8 - 68.4	7.9 - 59.9	0 - 40.6
Clinical Benefit Rate (CR + PR + SD)	**91.7%**	**73.3%**	**100%**	**81.8%**	
95% CI	63.4 - 99.6	46.5 - 90.3	68.4 - 100.0	50.0 - 96.7	

Enrichment of activity by wt CXCL12 3'UTR

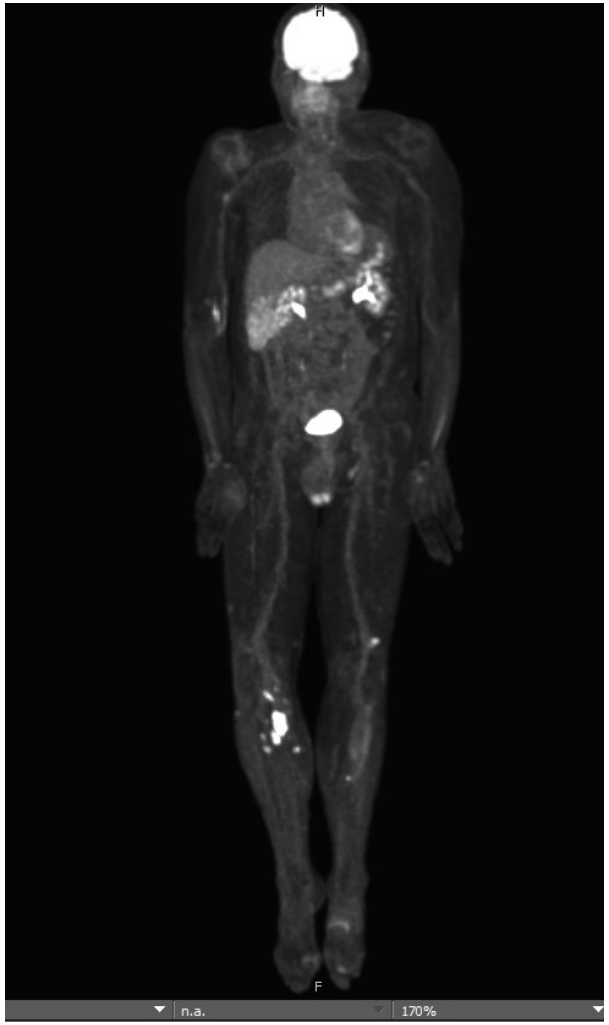
[1] Per protocol set – prespecified primary analysis population includes all pts who received at least 1 dose of tipifarnib and have 1 post-baseline tumor measurement

Preliminary data as of 24 May 2019

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



Baseline



End of Cycle 2

- 77 yo; PTCL-NOS Stage IV
- CHOP x 5 with response then PROG biopsy-proven PTCL relapse in multiple skin nodules
- Rapid PR after two cycles of tipifarnib

Proof of Concept for Tipifarnib in AITL

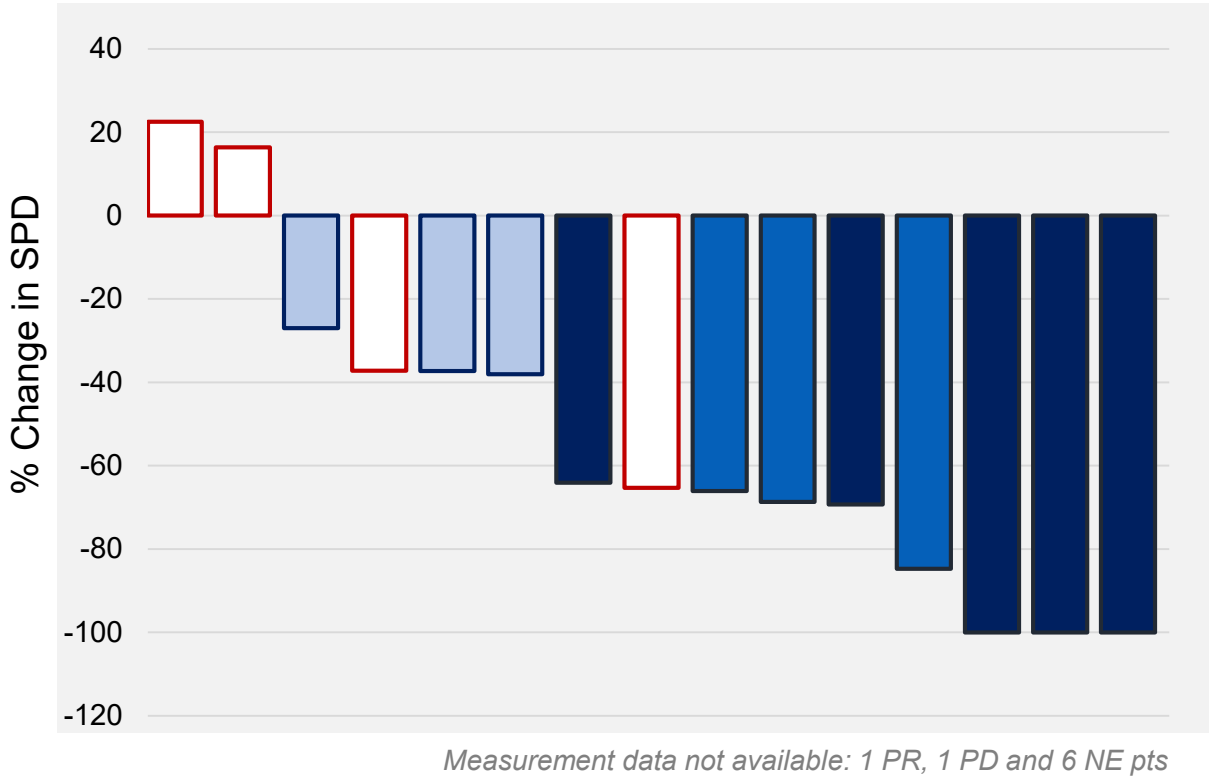
	AITL Cohort		All AITL in KO-TIP-002[1]	
Total treated	16		23	
Total efficacy evaluable	11		17	
Overall Best Response				
Complete Response (CR)	3		5	
Partial Response (PR)	2		4	
Stable Disease (SD)	3		3	
Progressive Disease (PD)	3		5	
Not efficacy evaluable (NE)	5		6	
	PPS[2]	mITT	PPS[2]	mITT
Overall 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

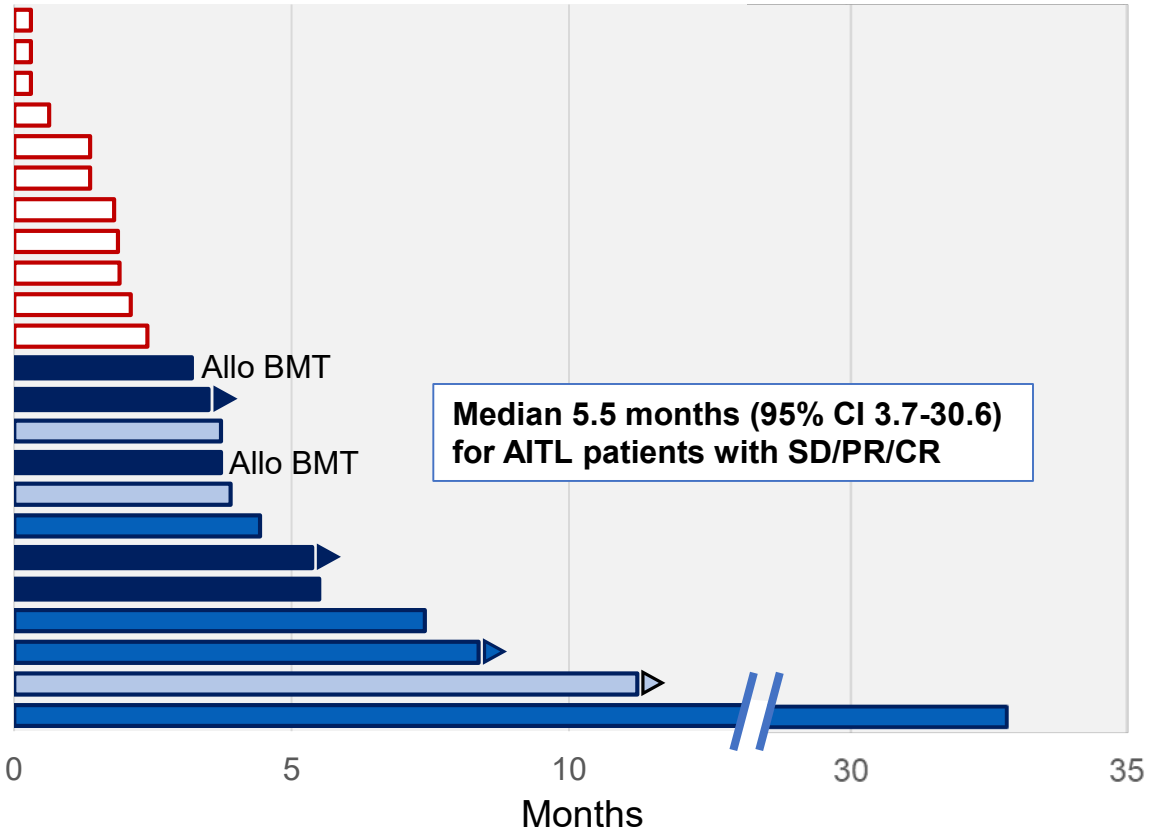
AITL: Tipifarnib treatment resulted in durable clinical responses and enabled subsequent transplant in patients achieving a CR

Maximum Change in Tumor Burden



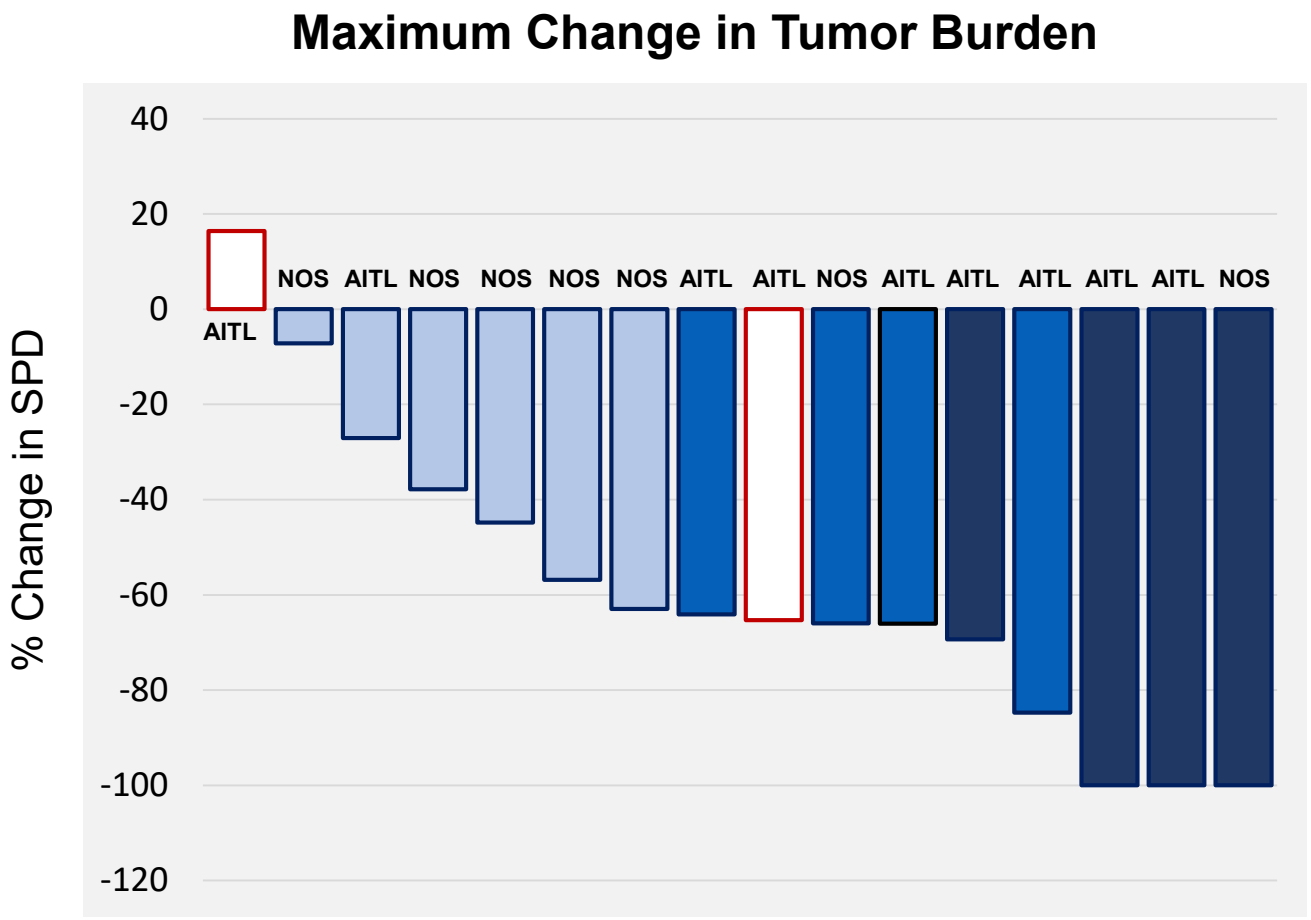
Measurement data not available: 1 PR, 1 PD and 6 NE pts

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

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

KIRs

Killer-cell immunoglobulin-like receptors (KIRs) are transmembrane glycoproteins expressed in NK and T cells that play key regulatory functions, including the control of chemokine/cytokine release and angiogenesis.

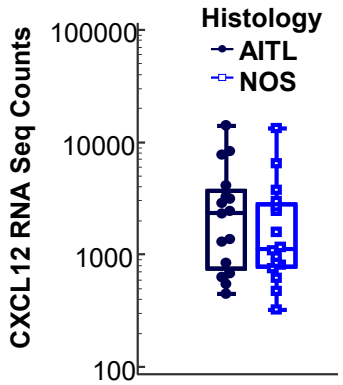
See poster at this meeting by A. Gualberto et al Abstract 156-P

Drivers of Tipifarnib's Activity

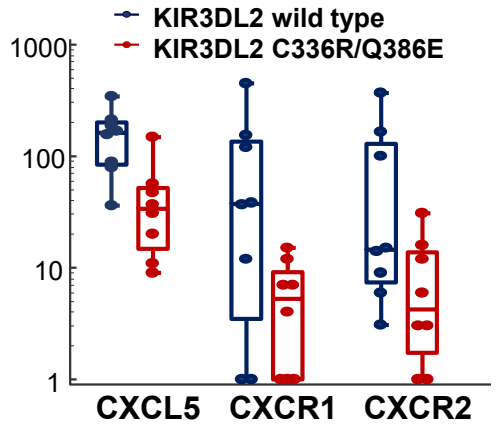
High CXCL12 expression, Low CXCL5 expression confer high clinical activity

AITL Genetics

High CXCL12 expression in AITL histology

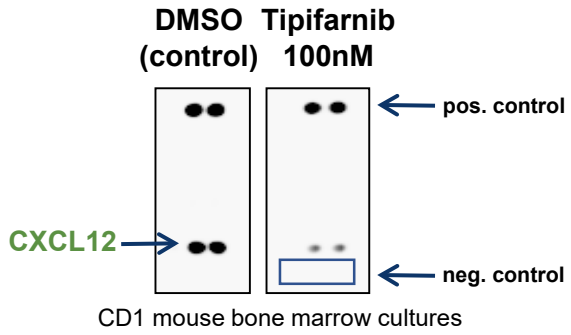


Low CXCL5 expression in KIR3DL2 mutant AITL

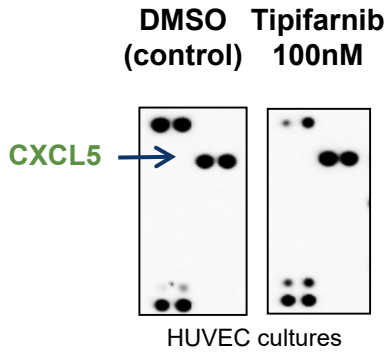


Mechanism of Action

Tipifarnib downregulates CXCL12 secretion

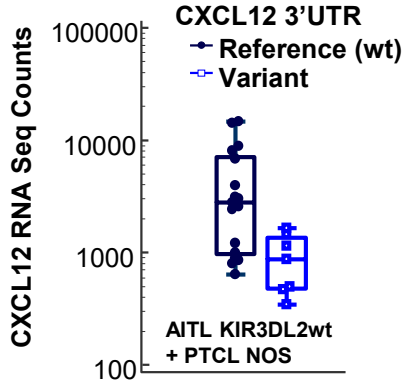


Tipifarnib does not inhibit CXCL5 secretion

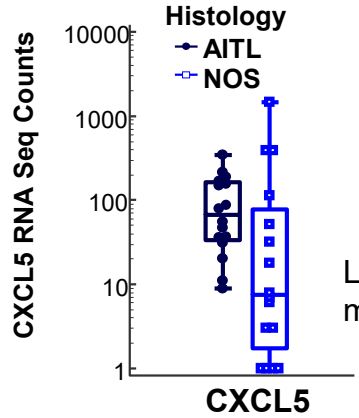


PTCL-NOS Genetics

High CXCL12 in subjects with wt CXCL12 3'UTR



Low CXCL5 expression in NOS



Low CXCL5 mediated resistance

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

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: 33.3% 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.

Acknowledgements

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