Proof of Concept for 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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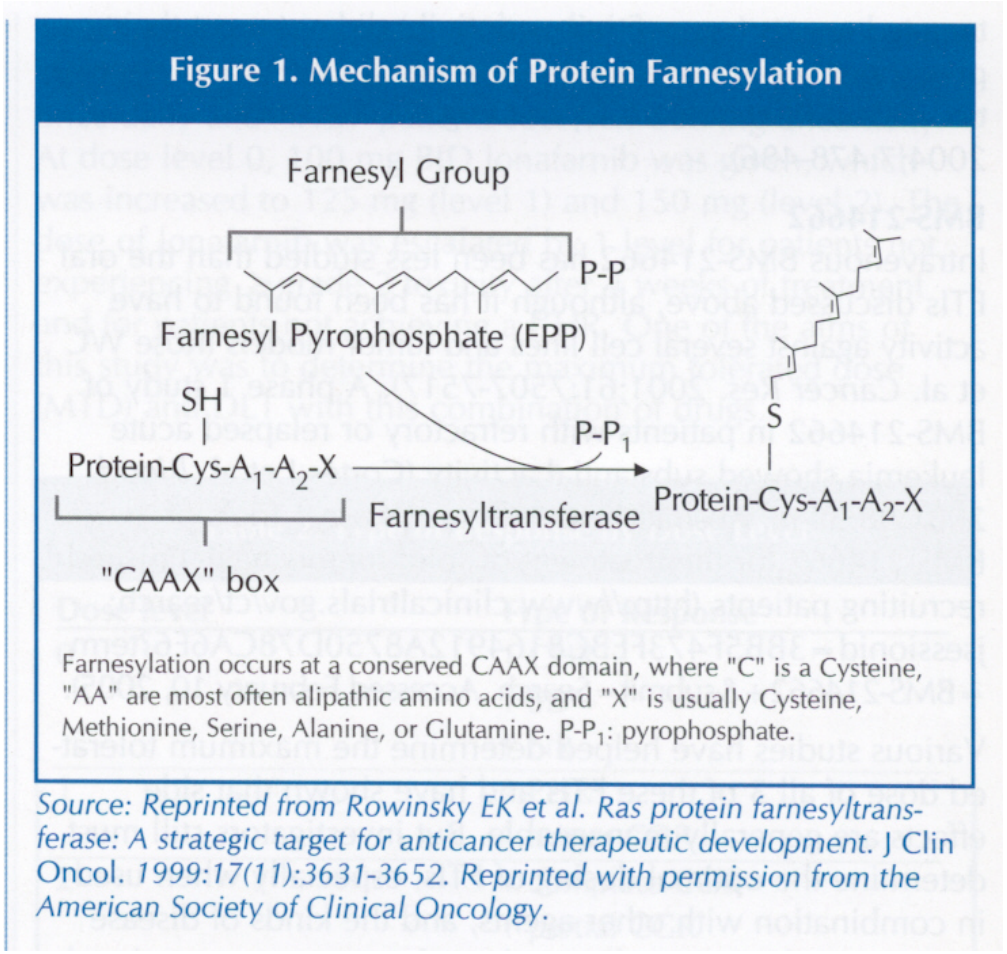
Tipifarnib is a Farnesyltransferase (FT) Inhibitor

- 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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Blood 2011 10.1182/blood-2011-02-334870

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

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Blood 2011 10.1182/blood-2011-02-334904

ORR in all 93 patients with different types of lymphoma = 20%

NCT00082888; LS038B Iowa/Mayo SPORE trial

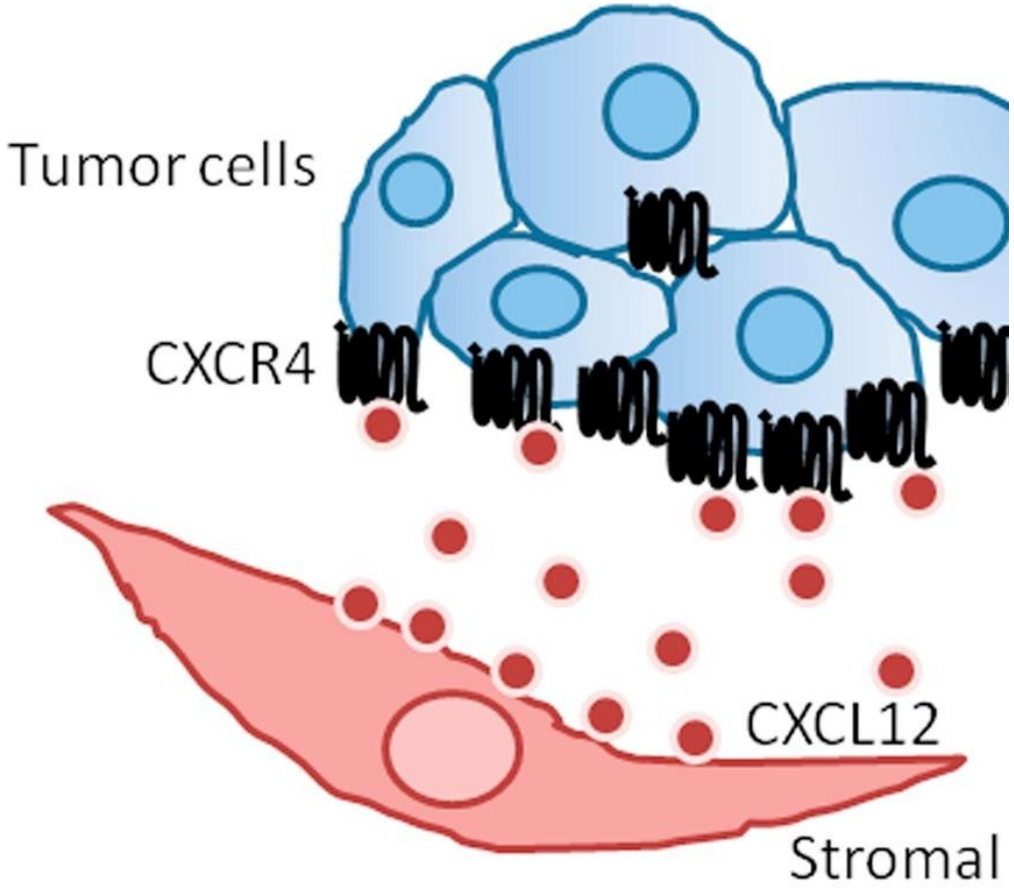
Development Path

- Studies in unselected patients with NHL, AML and solid tumors were not felt to be promising enough for registration
  - Drug development of Tipi and other FTI was halted
- Drug in licensed to Kura Oncology from Janssen
- Samples from previous studies were re-evaluated for new biomarkers that would predict for response
- New trials (KO-TIP-002) were designed to test this biomarker strategy

Goals of this Presentation

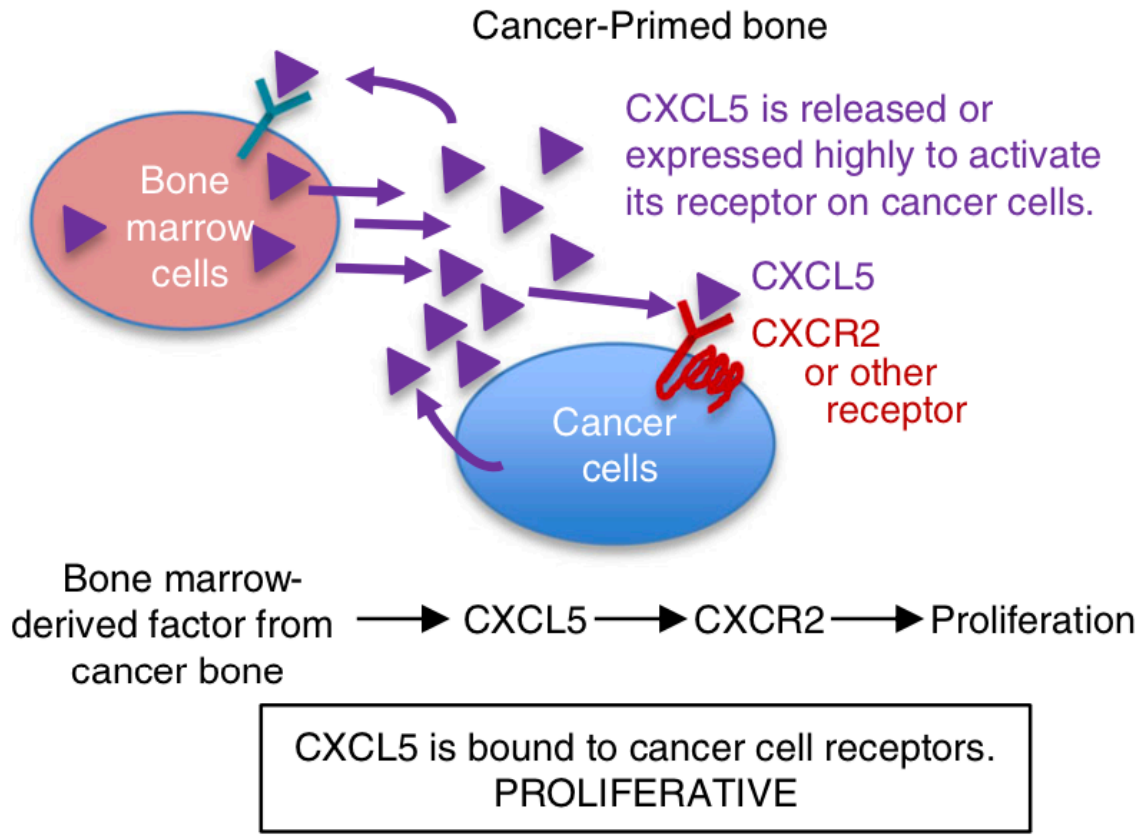
- To review data from this *new ongoing* phase 2 study (KO-TIP-002) of single-agent tipifarnib in T-cell lymphoma
  - Single-agent tipifarnib at a dose of 300 mg po bid days 1-21 q28 days
- Demonstrate how 3 biomarkers learned from unselected pts are being used prospectively to enrich the ORR to Tipifarnib
  - **CXCL12** expression and its receptor **CXCR4**
  - **CXCL5** expression and its receptor **CXCR2**
  - **KIR3DL2** variants in the tumor

CXCL12 expression and its receptor **CXCR4**



10.1016/j.ejpb.2017.07.003

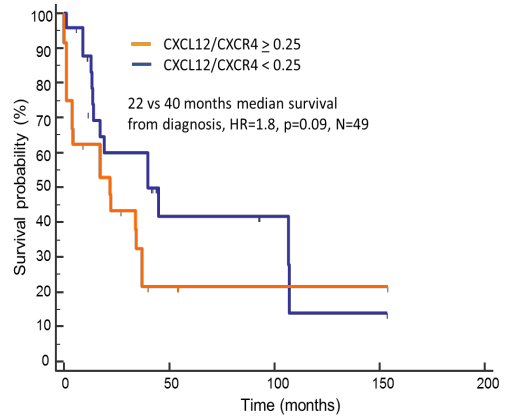
CXCL5 expression and its receptor **CXCR2**



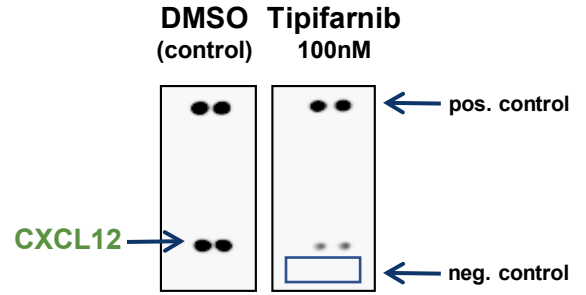
10.1038/s41467-019-12108-6

Tipifarnib is a CXCL12/CXCR4 Pathway Inhibitor

- **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**
  - Tipifarnib does not downregulate other chemokines such as CXCL5, and CXCL5 expressing AITL appears to be less sensitive to tipifarnib[3]



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



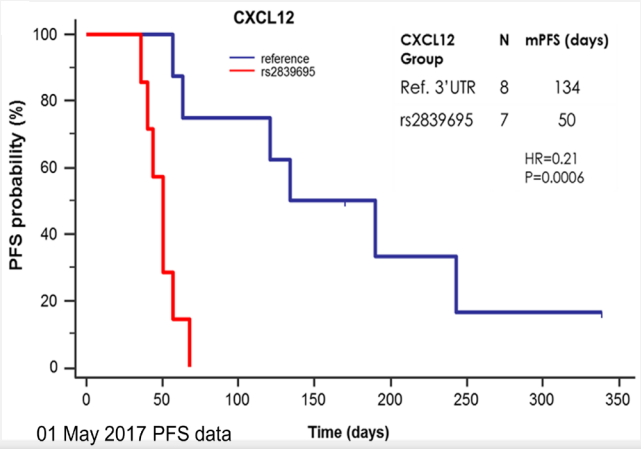
Tipifarnib downregulates the secretion of CXCL12 ex-vivo in CD1 mouse bone marrow cultures

[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

AITL Cohort (N = up to 20)

- 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%.

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%.

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

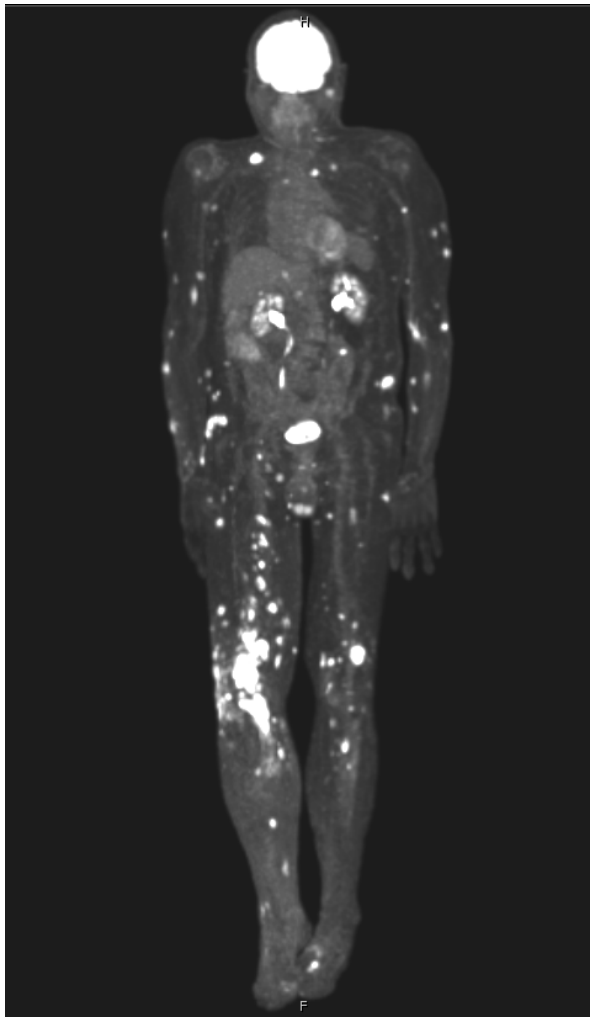
Proof of Concept for Tipifarnib in wt CXCL12 3'UTR PTCL

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

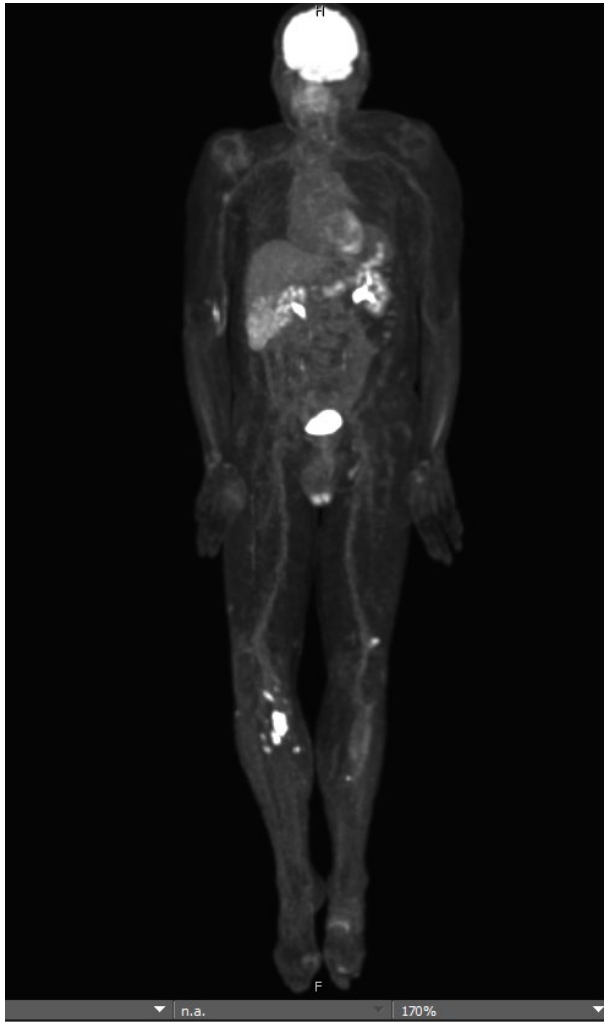
[1] Per protocol set – prespecified primary analysis population includes all pts who received at least 1 dose of tipifarnib and have 1 post-baseline tumor measurement

Preliminary data as of 24 May 2019

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

Demographics: All AITL Patients[1]

	Total
AITL Patients Treated[1], n (%)	**26 (100)**
AITL Patients Evaluable for Efficacy[2], n (%)	**20 (100)**
Age, yrs	
Median	**66.3**
Min, Max	**46, 87**
Male, n (%)	**17 (65)**
Female, n (%)	**9 (35)**
Number of Prior Anti-Cancer Regimens	
Median	**3**
Min, Max	**1, 7**
Prior ASCT, n (%)	**13 (50)**

Preliminary data as of 11 Nov 2019

[1] AITL patients were enrolled in stages 1 and 2 of the original protocol, in the AITL cohort, and the CXCL12+ PTCL cohort. Two additional AITL patients have been enrolled since data cutoff date.

[2] To be evaluable for efficacy, patient must have received at least 1 dose of tipifarnib and have at least 1 post baseline tumor response assessment

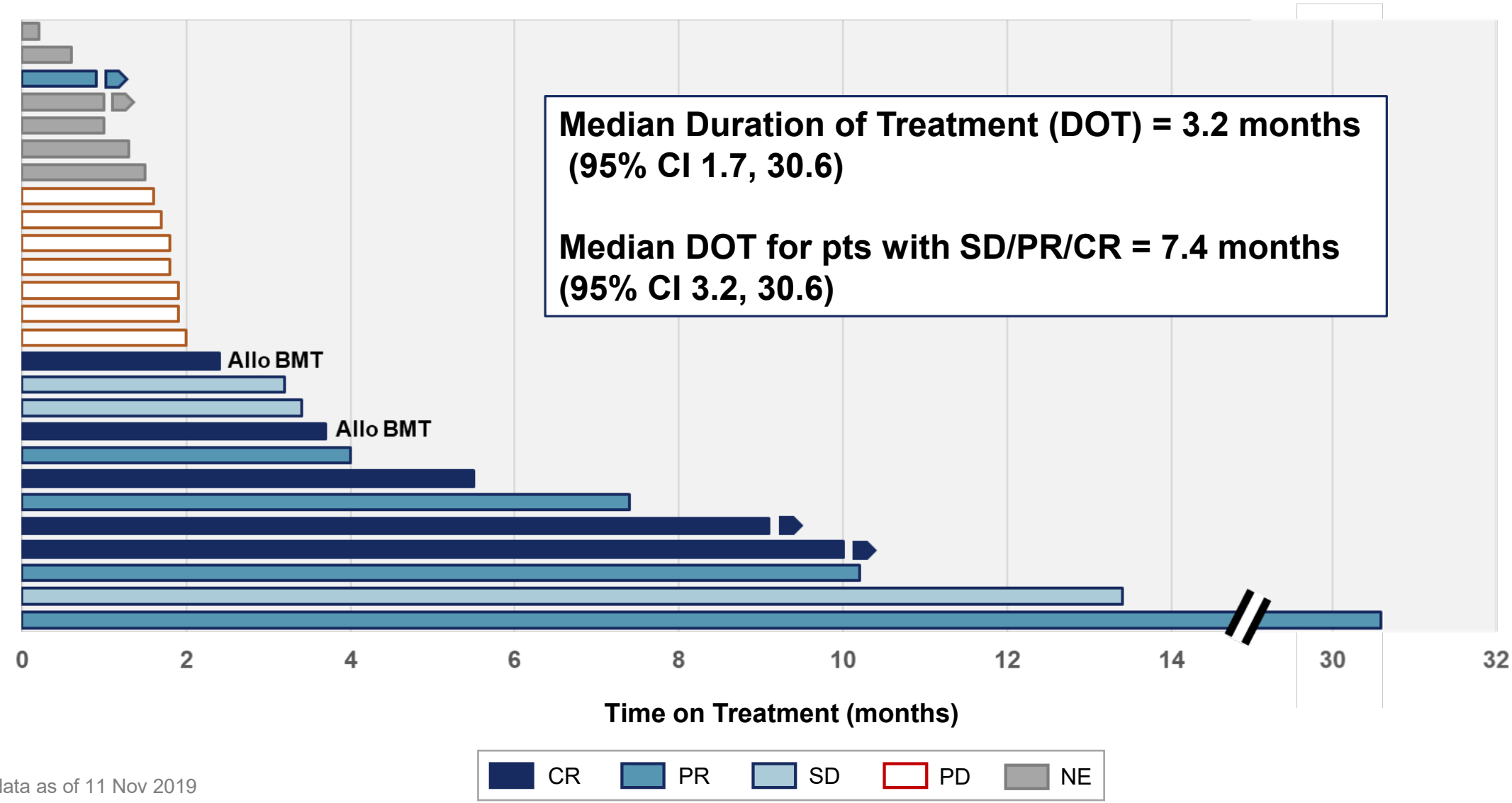
Proof of Concept of Tipifarnib in AITL

Total AITL pts treated	**26**	
Efficacy evaluable	**20**	
Overall Best Response		
Complete Response (CR)	**5**	
Partial Response (PR)	**5**	
Stable Disease (SD)	**3**	
Progressive Disease (PD)	**7**	
Not efficacy evaluable (NE)/Not yet evaluable	**5/1**	
	PPS[1]	**mITT**
Overall Response Rate (CR + PR)	**50%**	**38%**
95% CI	**(28%, 72%)**	**(20%, 59%)**
Clinical Benefit Rate (CR + PR + SD)	**65%**	**50%**
95% CI	**(44%, 86%)**	**(30%, 70%)**

Preliminary data as of 11 Nov 2019

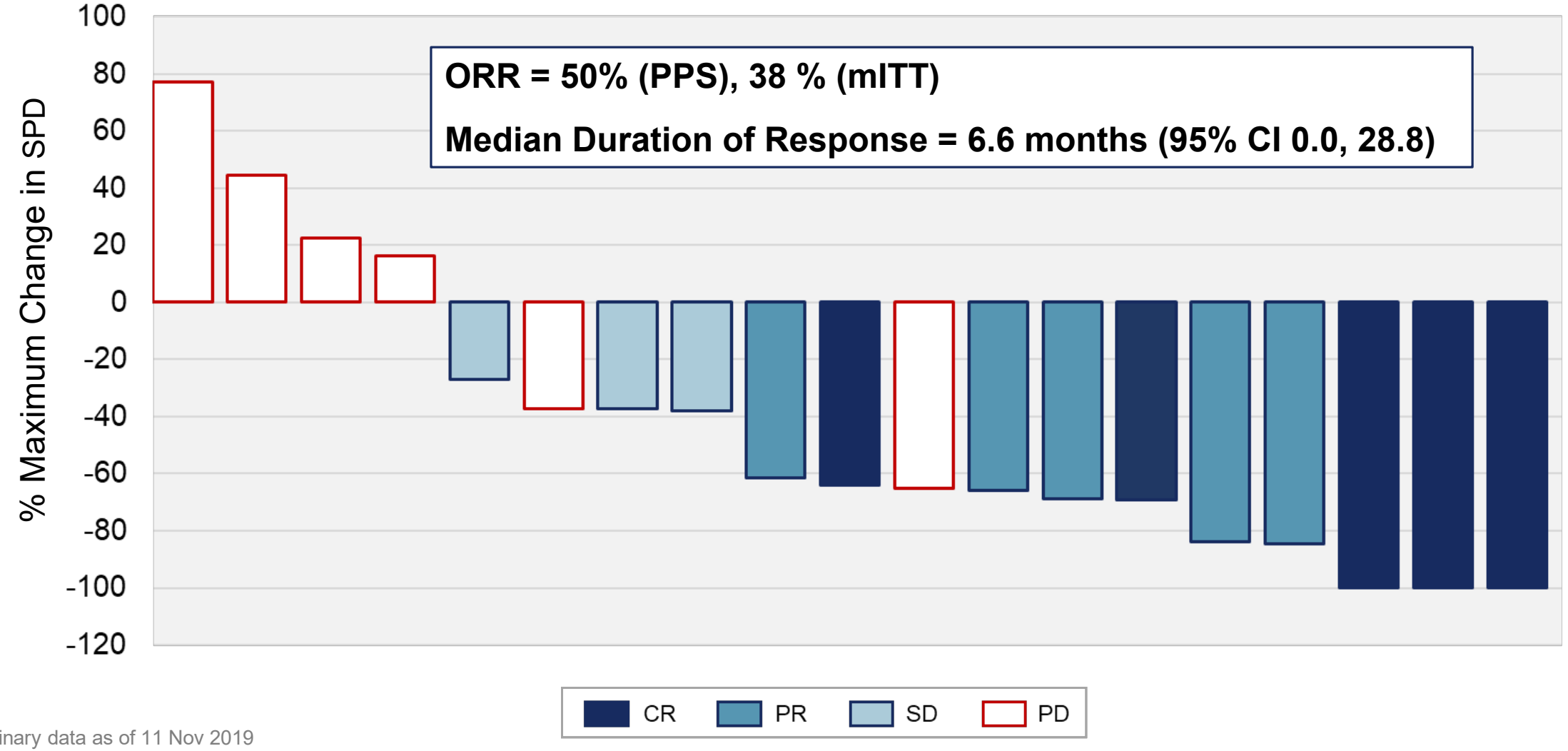
[1] Per protocol set – prespecified primary analysis population includes all pts who received at least 1 dose of tipifarnib and have 1 post-baseline tumor measurement.

Durable Clinical Responses with Tipifarnib in AITL



Preliminary data as of 11 Nov 2019

Significant Reduction in Tumor Burden with Tipifarnib Treatment

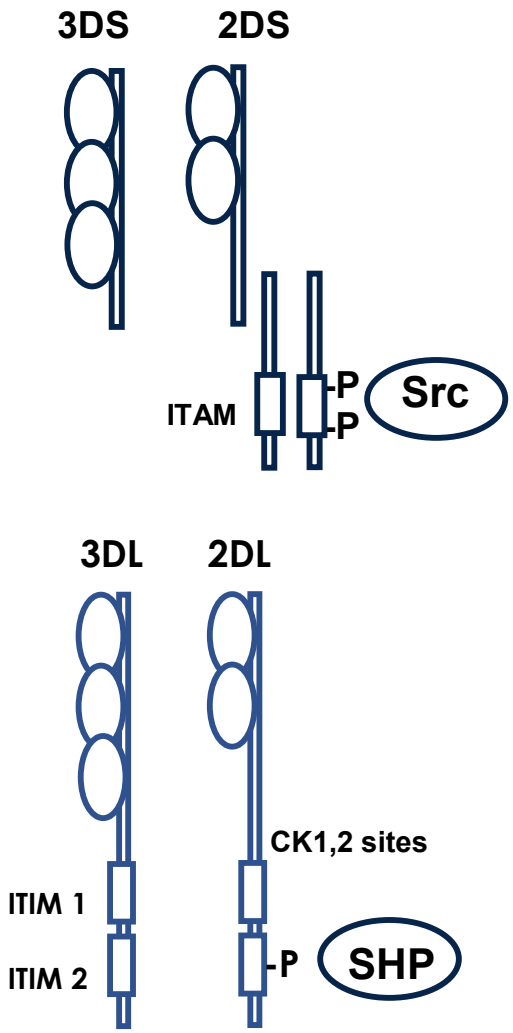


Preliminary data as of 11 Nov 2019
Measurement data not available: 1 PD and 6 NE pts

Using KIRs to Select Responders

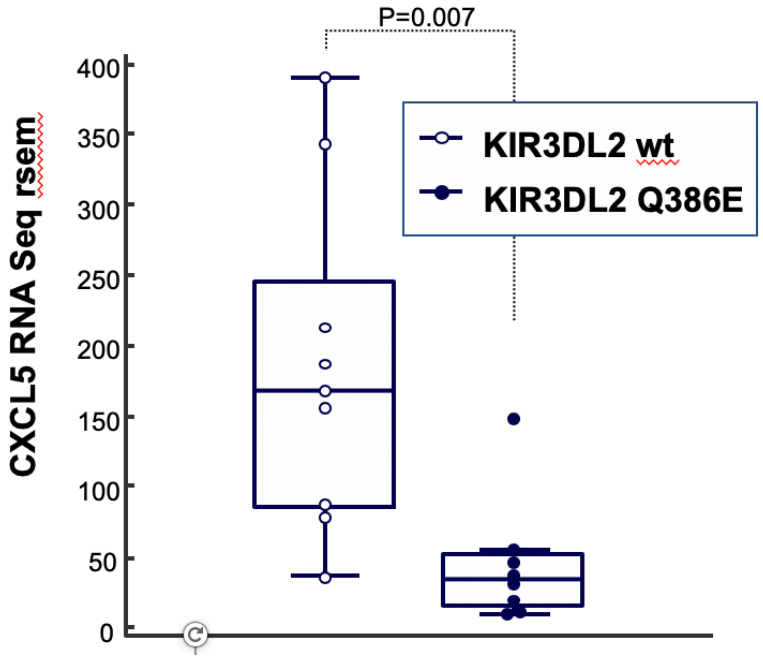
Killer Cell Immunoglobulin - Like Receptor (KIR)

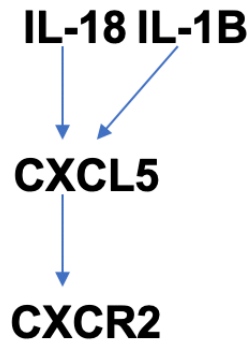
- KIRs = transmembrane glycoproteins expressed in NK/T cells
  - Control chemokine/cytokine release and angiogenesis.
- KIR-DS receptors signal intracellularly through ITAM motifs and Src
- KIR-DL receptors signal through ITIM motifs and SHP(s).
  - SHP(s) dephosphorylate Src phosphorylation targets.



KIR Variants are associated with Low CXCL5

- Structure and function of KIRs were evaluated in patient tumor samples.
- Expression of IL-18 and CXCL5 were significantly lower in AITL tumors carrying KIR3DL2 C336R/Q386E variants.
- CXCL5 is potentially a mechanism of resistance to tipifarnib.
- No effect of KIR3DL2 variants on CXCL12





High Activity of Tipifarnib in AITL with KIR3DL2 C336R/Q386E Variants

Ten of 19 DNA sequenced tumors carried C336R/Q386E gene variants of KIR3DL2 and were highly sensitive to tipifarnib.

	KIR3DL2 C336R/386E^	KIR3DL2 Wild Type
N	10	9
Overall Best Response		
CR	4	1
PR	3	1
SD	2	-
PD/NE	1	4/3*
ORR (mITT)	**70%**	**22%**
95% CI	**36 – 93%**	**28 – 60%**

KIR3DL2 C336R variant allele frequency (VAF) correlated with quality of response.

RESP.	KIR3DL2 C336R VAF
SD	43.9
CR	40.8
CR	39.1
CR	36.6
CR	33.3
PR	27
PR	22
SD	21.6
PR	20.9
PD	15

Preliminary data as of 11 Nov 2019.
^ Subjects carried both C336R and Q383E missense KIR3DL2 variants as determined by tumor NGS .
* One WT subject is pending first on-study efficacy assessment. VAF= variant allele frequency

Safety and tolerability of tipifarnib in AITL

- 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).

Grade 3 or Higher Study Drug Related TEAEs (≥ 10% pts)	
Patients With at Least One Gr 3 or Higher Related TEAE, n (%)	19 (73.1)
Thrombocytopenia	10 (38.5)
Neutropenia	8 (30.8)
Anemia	5 (19.2)
Leukopenia	4 (15.4)
Febrile neutropenia	3 (11.5)
Pancytopenia	3 (11.5)

Preliminary data as of 11 Nov 2019

Conclusions

- Tipifarnib is active in AITL pts; ORR = 50% (PPS), 38% (mITT)
- Patients with high CXCL12 expression and KIR3DL2 gene variants provide a robust tool for the selection/stratification of AITL patients; ORR = 70% (PPS/mITT).
- Side effects are similar to past experience and are primarily hematological events which may require dose modifications and/or supportive care.
- These data have informed the design of a single-arm tipifarnib monotherapy registration-directed trial in relapsed/refractory AITL and AITL-like histologies.
- Other CXCL12 indications, e.g. PTCL-NOS, CTCL and DLBCL, should be considered in future trials.

Acknowledgements

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