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Proof of Concept for Tipifarnib in Relapsed or Refractory Angioimmunoblastic T-cell Lymphoma (AITL): Preliminary Results from an Open-Label, Phase 2 Study

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BACKGROUND

- Tipifarnib is a CXCL12/CXCR4 pathway inhibitor
  - Downregulates CXCL12 secretion *ex vivo* in CD1 mouse bone marrow stroma cultures
  - Expression of uniquely farnesylated proteins (RhoE and PRICKLE2) is strongly associated with CXCL12 expression, suggesting potential CXCL12-related tipifarnib targets[1]
- CXCL12 and CXCL5 are chemokines essential for the trafficking of peripheral T cells to lymphoid organs and bone marrow and maintenance of immune cell progenitors; they function via the receptors CXCR4 and CXCR2, respectively[2]
- Up to 50% of patients with AITL and 35% of patients with peripheral T-cell lymphoma (not otherwise specified; PTCL-NOS) had a high CXCL12:CXCR4 expression ratio, which was associated with a negative prognosis in patients receiving standard-of-care therapy[3]

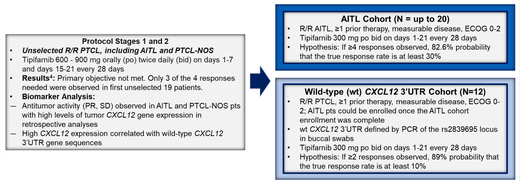
AIMS

- Herein we report preliminary efficacy, safety and biomarker data from a Phase 2 study of tipifarnib in patients with AITL

METHODS

- This Phase 2 study (NCT02464228) is a multi-institutional, single-arm, open-label trial evaluating the efficacy, safety, and biomarkers associated with tipifarnib treatment in patients with relapsed/refractory PTCL (**Figure 1**)

Figure 1. Study Design



AITL, angioimmunoblastic T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; PR, partial response; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; R/R, relapsed/refractory; SD, stable disease.

- Given the antitumor activity observed in the AITL population, enrollment was expanded to include up to 20 additional patients with tumors of AITL and related T follicular helper cell histologies
- Additionally, the study was amended to include a cohort of AITL and PTCL patients with the *CXCL12* rs2839695 A/A genotype (wild-type [wt] *CXCL12* 3'UTR cohort); target enrollment in the AITL and PTCL *CXCL12* 3'UTR cohorts was 12 patients each
- Patients were treated until progressive disease (PD) or unacceptable toxicity
- The primary endpoint of the study was ORR
- Oncogene sequencing of tumor tissue samples was performed using RNA-Seq

RESULTS

Patients

- As of 11 November 2019, 53 patients with PTCL have been treated with tipifarnib (stages 1 and 2, n=19; AITL extension cohort, n=19; wt *CXCL12* 3'UTR cohort, n=15)
  - Among these patients, 26 had AITL (stages 1 and 2, n=3; AITL extension cohort, n=19; wt *CXCL12* 3'UTR cohort, n=4; **Table 1**)

TABLE 1. PATIENT DEMOGRAPHICS

	Total
AITL patients treated[a], n (%)	26 (100)
AITL patients evaluable for efficacy[b], n (%)	20 (100)
Age, years	
Median	66.3
(Range)	(46-87)
Gender	
Male, n (%)	17 (65)
Prior anticancer regimens, n	
Median	3
(Range)	(1-7)
Recieved prior ASCT, n (%)	13 (50)

[a]Patients with AITL were enrolled in stages 1 and 2 of the original protocol, in the AITL cohort, and in the wt *CXCL12* 3'UTR cohort. Two additional AITL patients have been enrolled since the data cutoff date.
[b]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.
AITL, angioimmunoblastic T-cell lymphoma; ASCT, autologous stem cell transplant.

Efficacy

- In PTCL-NOS, patients with a *CXCL12* 3'UTR gene variant did not demonstrate any response to tipifarnib, in contrast to patients with wt *CXCL12* 3'UTR, for whom the ORR for the per-protocol set (PPS) was 33.3% (**Table 2**)

TABLE 2. PROOF OF CONCEPT FOR TIPIFARNIB IN WT *CXCL12* 3'UTR PTCL-NOS

	wt *CXCL12* 3'UTR cohort: PTCL-NOS		Variant *CXCL12* 3'UTR PTCL-NOS enrolled in stage 1/2
Total treated	11		6
Total efficacy evaluable	9		6
Overall Best Response			
CR	1		0
PR	2		0
SD	6		0
PD	0		6
NE	2		0
	PPS[a]	**mITT**	**PPS/mITT**
ORR[b], % (95% CI)	33.3 (9.8, 68.4)	27.3 (7.9, 59.9)	0 (0, 40.6)
Clinical benefit rate[c], % (95% CI)	100 (68.4, 100.0)	81.8 (50.0, 96.7)	0

[a]Per-protocol set, the prespecified primary analysis population that includes all patients who received at least 1 dose of tipifarnib and have 1 post-baseline tumor measurement.
[b]Defined as the percentage of patients with a CR or PR.
[c]Defined as the percentage of patients with a CR, PR, or SD.
CR, complete response; mITT, modified intent-to-treat; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; PTCL-NOS, peripheral T-cell lymphoma (not otherwise specified); SD, stable disease; wt, wild-type.

- Among the 20 efficacy-evaluable patients with AITL, 10 objective responses (ORR, 50%; complete response [CR], n=5; partial response [PR], n=5) occurred (**Table 3**)

RESULTS (CONT.)

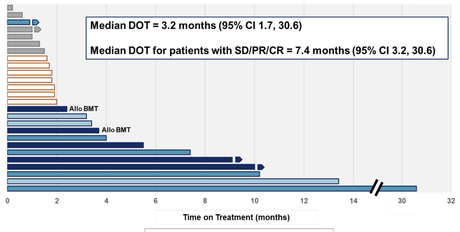
TABLE 3. SUMMARY OF RESPONSES IN TIPIFARNIB-TREATED PATIENTS WITH AITL

	Patients	
Total AITL patients treated, n	26	
Efficacy evaluable, n	20	
Overall best response, n		
CR	5	
PR	5	
SD	3	
PD	7	
NE/not yet evaluable	5/1	
	PPS[a]	**mITT**
ORR[b], % (95% CI)	50 (28, 72)	38 (20, 59)
Clinical benefit rate[c], % (95% CI)	65 (44, 86)	50 (30, 70)

[a]The prespecified primary analysis population that includes all patients who received at least 1 dose of tipifarnib and had 1 post-baseline tumor measurement.
[b]Defined as the percentage of patients with a CR or PR.
[c]Defined as the percentage of patients with a CR, PR, or SD.
AITL, angioimmunoblastic T-cell lymphoma; CR, complete response; mITT, modified intent-to-treat; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PPS, per protocol set; PR, partial response, SD, stable disease.

- Overall, the median duration of response was 6.6 months
- In patients demonstrating a clinical benefit, the median duration of treatment was 7.4 months (**Figure 2**)
  - Two patients who had a CR proceeded to allogeneic bone marrow transplant

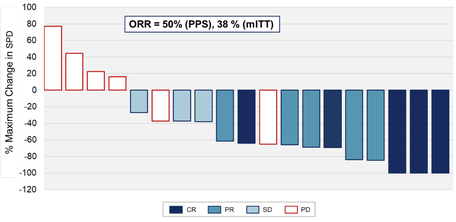
Figure 2. Duration of Tipifarnib Treatment in Patients with AITL



AITL, angioimmunoblastic T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; PR, partial response; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; R/R, relapsed/refractory; SD, stable disease.

- There was a reduction in tumor burden with tipifarnib treatment (**Figure 3**)

Figure 3. Change in Tumor Burden in Tipifarnib-Treated Patients[a]



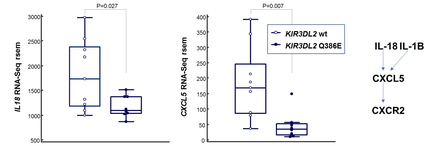
[a]Measurement data were not available for one patient with PD and six NE patients.
CR, complete response; mITT, modified intent-to-treat; NE, non-evaluable; ORR, overall response rate; PD, progressive disease; PPS, per-protocol set; PR, partial response; SD, stable disease; SPD, sum of the products of diameters.

RESULTS (CONT.)

Biomarker Analysis

- A strong association between *KIR3DL2* C336R/Q386E mutation and the activity of tipifarnib was observed in patients with AITL
  - Expression of *CXCL5* and *IL18* was significantly lower in AITL tumors carrying *KIR3DL2* C336R/Q386E variants (**Figure 4**)
  - There was no effect of *KIR3DL2* variants on *CXCL12* expression
- CXCL12/CXCR4 and CXCL5/CXCR2 appear to drive sensitivity and resistance to tipifarnib, respectively
- Tipifarnib strongly downregulates *CXCl12* but does not affect *CXCL5*
- Low levels of CXCL5 in tumors with KIR3DL2 variants may explain sensitivity to tipifarnib

Figure 4. Expression of *IL18* and *CXCL5* in wt and Q386E *KIR3DL2* patients



- *KIR3DL2* C336R/Q386E variants were present in 10 of the 19 patients with sequencing data. These patients were highly sensitive to tipifarnib, with 7/10 experiencing an objective response (**Table 4**).
  - *KIR3DL2* C336R variant allele frequency correlated with the quality of response

TABLE 4. ACTIVITY OF TIPIFARNIB IN PATIENTS WITH AITL AND *KIR3DL2* C336R/Q386E VARIANTS

	KIR3DL2 C336R/386E[a] (n=10)	*KIR3DL2* wt (n=9)
Overall best response		
CR	4	1
PR	3	1
SD	2	-
PD/NE	1	4/3[b]
ORR (mITT), % (95% CI)	70 (35, 93)	22 (28, 60)

Response	*KIR3DL2* C336R VAF
SD	49.9
CR	40.8
CR	39.1
CR	36.6
CR	33.3
PR	27
PR	22
SD	21.6
PR	20.9
PD	15

[a]Patients carrying both C336R and Q383E missense *KIR3DL2* variants as determined by tumor next-generation sequencing.
[b]One wt patient is pending first on-study efficacy assessment.
mITT, modified intent-to-treat; VAF, variant allele frequency; wt, wild-type.

Safety

- All patients with AITL had at least one treatment-emergent adverse event (TEAE)
  - In total, 24 (92.3%) patients had at least one study drug-related TEAE, and seven (26.9%) had at least one study drug-related SAE
- One study drug-related death (lung infection) was reported
- The most common treatment-related TEAEs were hematological in nature (**Table 5**)

RESULTS (CONT.)

TABLE 5. GRADE 3 OR HIGHER STUDY DRUG-RELATED TEAES OCCURRING IN ≥10% OF PATIENTS

	Patients (N=26)
At least one, 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)

- Four patients (15.4%) discontinued due to TEAEs, which included one case each of hemolytic anemia, pancytopenia, lung infection, cardiopulmonary failure, and dyspnea (one patient experienced more than one TEAE leading to discontinuation)

CONCLUSIONS

- Tipifarnib is active in patients with AITL: ORR = 50% (PPS), 38% (mITT)
- High *CXCL12* expression and presence of *KIR3DL2* gene variants provide a robust tool for the selection/stratification of patients with AITL: ORR = 70% (PPS/mITT)
- Adverse events were similar to past experience and were primarily hematological events, which may require dose modifications and/or supportive care
- These data could inform the design of a single-arm tipifarnib monotherapy registration-directed trial in relapsed/refractory AITL and AITL-like histologies
- Other CXCL12 indications (eg, PTCL-NOS, cutaneous T-cell lymphoma, and diffuse large B-cell lymphoma) should be considered in future trials

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