Final Results from KO-TIP-002 a Phase 2 Study of Tipifarnib in Subjects with Relapsed or Refractory Peripheral T-Cell Lymphoma (NCT02464228)

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Disclosure

- Clinical trial support from Kura Oncology

Tipifarnib

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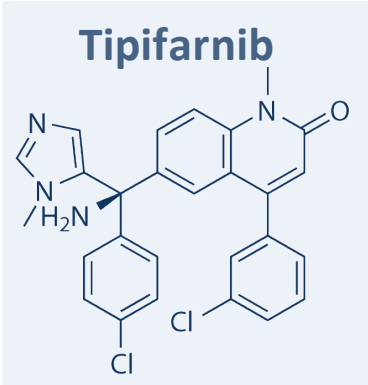
- Tipifarnib is a potent, oral farnesyltransferase inhibitor
- In-licensed to Kura Oncology from Janssen
- Well characterized and manageable safety profile
  - (> 5,000 patients treated by Janssen program)
- Two different schedules have emerged:
  - 300 mg po bid days 1-21 q28 days
  - 600 - 900 mg po bid days 1-7 and days 15-21 q28 days



Tipifarnib in a Previous Phase 2 Trial in the Lymphoma SPORE

Disease Type	N (%)	ORR %	Median DOR (Months)
All Patients	93	20	7.5 (4.9-18.5)
Aggressive B	42	17	11.3 (4.9-17.1)
Indolent B	15	7	2 (NR)
Hodgkin/T-cell	36	31	7.5 (3.2-29.8)
Hodgkin	19	21	NA*
T-cell	17	41	NA*

*Not applicable

Blood. 2011; 118(18):4882-4889

blood

2011 118: 4882-4889
Prepublished online July 1, 2011;
doi:10.1182/blood-2011-02-334904

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

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

blood

2011 118: 4872-4881
Prepublished online June 14, 2011;
doi:10.1182/blood-2011-02-334870

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

Husheng Ding, Jennifer Hackbarth, Paula A. Schneider, Kevin L. Peterson, X. Wei Meng, Haiming Dai, Thomas E. Witzig and Scott H. Kaufmann

PO Tipifarnib 300 mg bid days 1-21 q28

Goals of Tipifarnib KO-TIP-002 Trial

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- Multi-center phase 2; Kura Oncology sponsored
- Test oral tipifarnib as a single-agent for relapsed/refractory T-cell non-Hodgkin lymphoma
- Optimize dosing strategy for lymphoma
- Test a new biomarker strategy based on tumor mutations

  - Earlier analysis (ASH2019) linked the mRNA expression of CXCL12 and the frequency of KIR variants to the response to tipifarnib; however mature data did not show a strong correlation with clinical response

Patient Eligibility

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1. ≥18 years of age.
2. Relapsed or refractory to at least 1 prior systemic cytotoxic therapy.
3. Must have received conventional therapy as a prior therapy.
4. Measurable disease according to the Lugano Classification and/or mSWAT.
5. Acceptable liver and renal function; and acceptable hematologic status.
6. 8 PTCL subtypes were allowed to enroll: ALCL- ALK positive or ALK negative, AITL, PTCL – NOS, Enteropathy-associated T-cell lymphoma, Extranodal natural killer (NK) T-cell lymphoma, nasal type, Hepatosplenic T-cell lymphoma,, Subcutaneous panniculitis-like T-cell lymphoma

Tipifarnib Drug Administration

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- Safety set (Total=65)
- Response set (Total = 58 evaluable): 32 AITL, 24 PTCL-NOS and 1 ALCL-ALK negative and 1 PTCL-subtype not specified by protocol
- Dosing schedules (2016-2021):
  - Tipifarnib 600 - 900 mg orally (po) twice daily (bid) on days 1-7 and days 15-21 every 28 days; N=20
  - Tipifarnib 300 mg orally (po) twice daily (bid) for 21 days in 28-day treatment cycles; N=45
- Median #cycles was 3 (2, 7) (median Q1,Q3)
- Mean dose intensity per cycle was 85%

Demographics and Prior Therapies

	PTCL-NOS*	AITL	Total **
Patients Treated (Safety Cohort)	25	38	65
Age, yrs, Median (Min, Max)	67 (31, 88)	66 (41, 87)	66 (31, 88)
Male, n (%)	18 (72)	22 (58)	41 (63)
Prior Anti-Cancer Regimens, Median (Min, Max)	3 (1, 8)	3 (1, 7)	3 (1, 8)
Belinostat, n (%)	4 (16)	2 (5)	6 (9)
Brentuximab Vedotin, n (%)	5 (20)	5 (13)	11 (17)
Romidepsin, n (%)	8 (32)	8 (21)	18 (28)
Prior ASCT***, n (%)	8 (32)	17 (45)	25 (38)

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***Excluded from analysis**: No baseline data; Failure to receive at least one dose of Tipifarnib; or No post-baseline endpoint data subsequent to at least 1 dose of study drug.*

* PTCL-NOS = Unselected PTCL-NOS + PTCL-NOS-CXCL12+

*** Includes 2 patients from "Other cohort" = ALCL-ALK- and PTCL-subtype not specified per protocol.*

*** ASCT = autologous stem cell transplant

Response to Tipifarnib in Relapsed PTCL: Trial 002

Cohort	PTCL-NOS*, N=24 % (n)	AITL, N = 32 % (n)	Total**, N = 58 % (n)
Primary: Overall Response CR + PR Rate	21 (5)	56 (18)	40 (23)
Complete Response	4 (1)	28 (9)	17 (10)
Partial Response	17 (4)	28 (9)	22 (13)
Stable Disease	38 (9)	9 (3)	21 (12)
Progressive Disease	38 (9)	34 (11)	38 (22)
Non-Evaluable	4 (1)	0	2 (1)
Secondary: mDOR (months)	2.0	7.8	4.6
mPFS (months)	NA	3.6	3.5

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Anti-tumor Activity of Tipifarnib in PTCL assessed according to the Lugano Classification
(Cheson et al. J Clin Oncol. 2014)

* PTCL-NOS = Unselected PTCL-NOS + PTCL-NOS-CXCL12+
*** Includes 2 patients from "Other cohort" = ALCL-ALK- and PTCL-subtype not specified per protocol*
mDOR=median Duration of Response, mPFS= median Progression Free Survival, NA: Not available

Patients still on drug (compassionate use)
AITL: 2 CR, 19 and 32 months
PTCL-NOS: 1 CR, 40 months

Significant Reduction in Tumor Burden with Tipifarnib Treatment – All Patients

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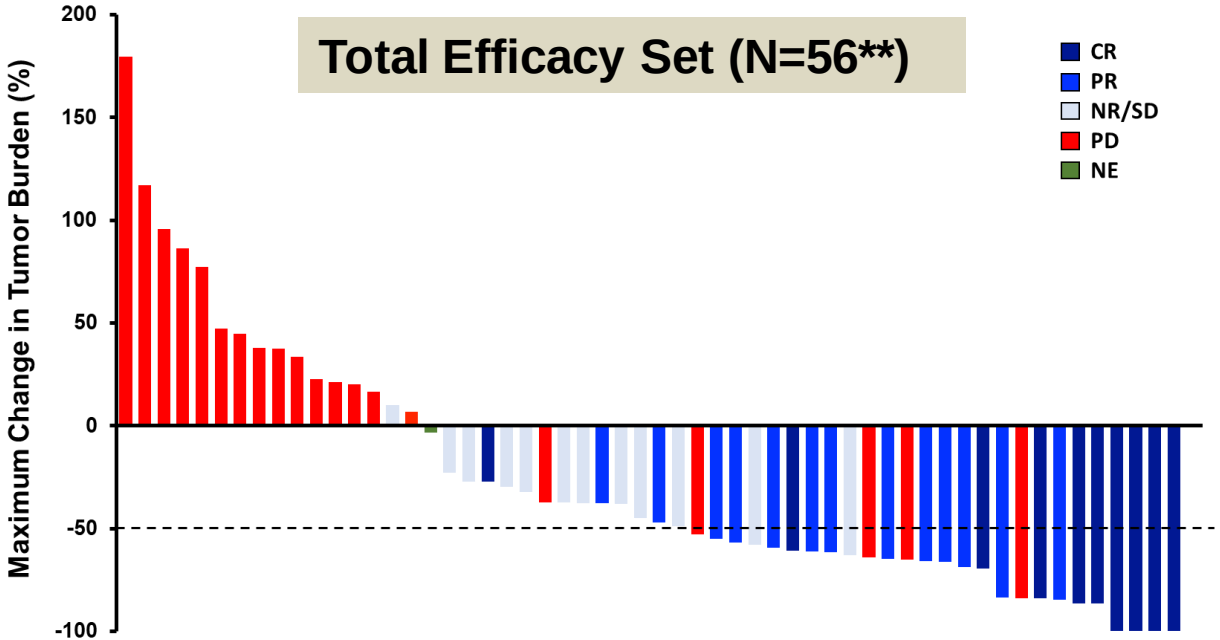
Greatest Percent Change in SPD* with Best Response



Disease Response Assessments: Screening, Day 22 (+/- 5 days) during cycles 2-6, then every 12 weeks until progression.

** SPD = Sum of product of Longest Diameter and Shortest Diameter of all tumors assessed in each visit in square mm*

**Two subjects that did not have post baseline index lesion measurements were excluded

Significant Reduction in Tumor Burden with Tipifarnib Treatment – AITL Patients

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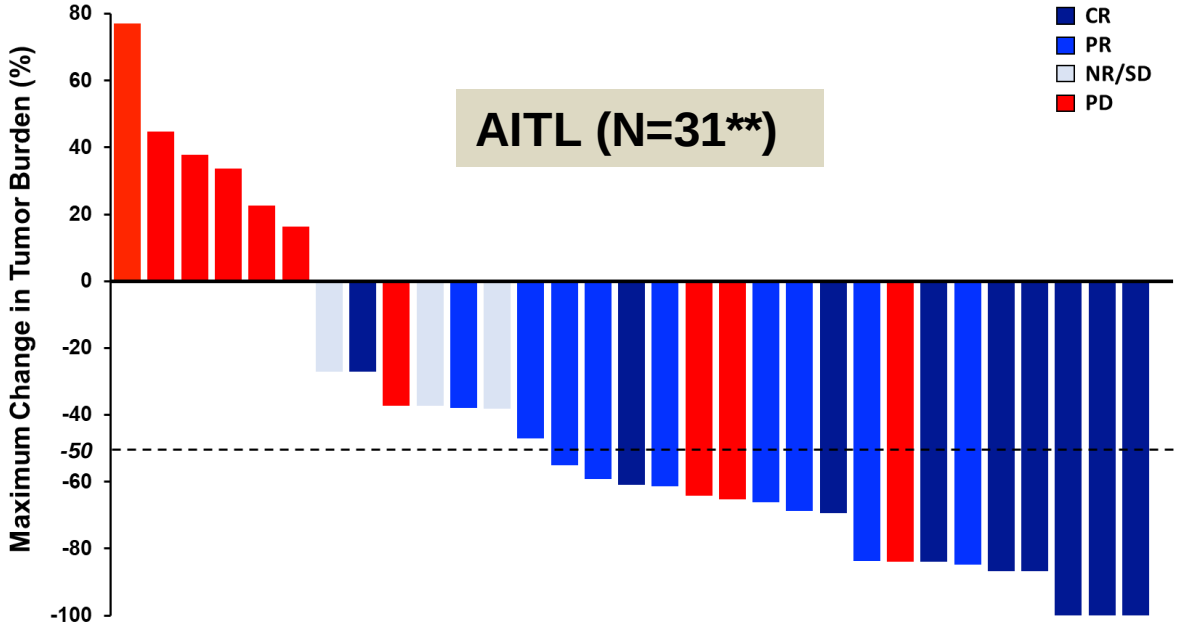
Greatest Percent Change in SPD* with Best Response



Disease Response Assessments: Screening, Day 22 (+/- 5 days) during cycles 2-6, then every 12 weeks until progression.

* SPD = Sum of product of Longest Diameter and Shortest Diameter of all tumors assessed in each visit in square mm

** One subject is excluded as they did not have post baseline index lesion measurements

TIP002: Biomarkers of Response to Tipifarnib

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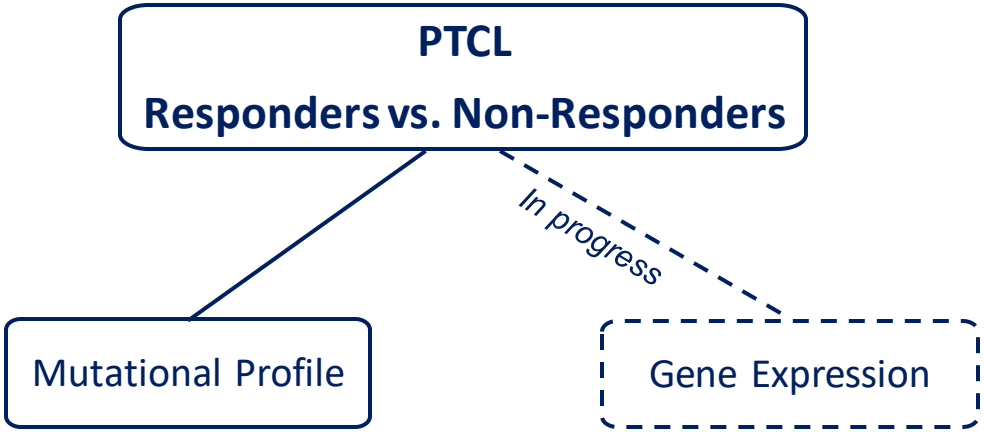
- Retrospective – pre-treatment- FFPE (or new biopsy)
- Central testing by Q2 solutions/EA Genomics
- RNA seq and Whole exome sequencing (WES)



TIP002: Mutational Profile of Key PTCL genes

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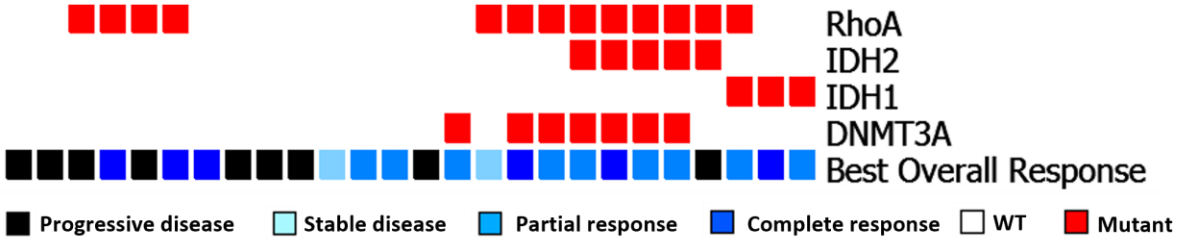
Retrospective analysis of 26 of 32 AITL available samples



- TET2 alteration were seen in 81% (21/26) and did not correlate with response.
- 62% (16/26) had mutations in any of the 4 key genes
  - 75% (12/16) had a response
- 38% (10/26) of tumors did not have a mutation in any of the 4
  - 30% (3/10) responded to Tipifarnib

Response to Tipifarnib is higher in AITL patients harboring the mutations in AITL subtype

** Functionally deleterious mutations – not accounting for SNPs*

NCCN Recommended Second Line Therapies for PTCL

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	Overall PTCL					AITL- specific				
Drugs	**N****	**ORR**	**CR & PR**	**mDOR (Months)**	**mPFS (Months)**	**N****	**ORR**	**CR & PR**	**mDOR (Months)**	**mPFS (Months)**
Belinostat	120	26%	CR 13% PR 18%	13.6	1.6	22	46%	CR 18% PR 28%	--	5.8
Romidepsin*	130	25%	CR 15% PR 10%	28	3.8	27	30%	CR 19% PR 11%	--	--
Pralatrexate	109	27%	CR 8% PR 18%	9.4	3.5	13	8%	--	--	--
Brentuximab Vedotin	34	41%	CR 24% PR 18%	--	--	13	54%	CR 38% PR 15%	--	6.7

*Romidepsin R/R PTCL accelerated approval withdrawn from FDA Aug. 2021 but remains in NCCN guidelines
**Efficacy evaluable patients

Blood. 2014 May 15; 123(20): 3095–3100., Hematol Oncol. 2017 Dec; 35(4): 914–917., https://beleodaq.com/uploads/PI-BELEODAQ-200120.pdf, http://www.folotyn.com/wp-content/uploads/2019/11/Folotyn-PI-09-2020-REF-0255.pdf, https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf

Safety Analysis

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- N= all 65 patients
  - 38 AITL
  - 25 PTCL-NOS
  - 1 ALCL-ALK negative
  - 1 PTCL-subtype not specified by protocol
- Related to study drug
  - 32% (21/65) dose reductions.
  - 20% (13/65) discontinuations.
- Toxicities were consistent with the known safety profile of tipifarnib.

Safety Profile – TEAEs observed in ≥20% patients

			Total*
TEAE n (%)			65 (100)
Study drug related TEAEs n (%)			57 (88)
Serious TEAEs n (%)			38 (59)
Study drug related Serious TEAEs n (%)			18 (28)
Grade 3 TEAE n (%)			54 (83)
System organ class	**Grades 1-2**	**Grades 3-4**	**Total***
Gastrointestinal disorders, n (%)	40 (62)	8 (12)	48 (74)
Diarrhoea	21 (32)	4 (6)	25 (39)
Nausea	25 (39)	0	25 (39)
Vomiting	13 (20)	1 (2)	14 (22)
Blood and lymphatic system disorders, n (%)	4 (6)	43 (66)	47 (72)
Neutropenia	4 (6)	29 (45)	33 (51)
Thrombocytopenia	4 (6)	29 (45)	33 (51)
Anaemia	11 (17)	18 (28)	29 (45)
Leukopenia	2 (3)	12 (19)	14 (22)
General disorders and administration site conditions, n (%)	38 (59)	9 (14)	47 (72)
Fatigue	19 (29)	5 (8)	24 (37)

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TEAE: treatment emergent adverse event

*Safety evaluable patients N=65

Version 19.0 of MedDRA was used to code AE

TIP002: Conclusion

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Safety

- Treatment with tipifarnib 300 mg bid on days 1-21 of 28-day cycles was generally well tolerated.
- TEAEs were consistent with the known safety profile of tipifarnib.

Efficacy in relapsed/refractory disease

- **PTCL (PTCL-NOS + AITL)**: An ORR of 40%, including 17% complete responses, was achieved in patients with R/R PTCL.
  - Further biomarker analysis ongoing in PTCL-NOS group
- **AITL:** Tipifarnib achieved an ORR of 56%, including 28% complete responses, in unselected patients
  - 75% ORR if the tumor had a responder mutation (DNMT3A, IDH1/2 and RhoA genes)

TIP002: Future Directions

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- Further biomarker research will investigate genomic signatures of response using RNAseq data to better define genetic mechanisms of primary and acquired resistance to tipifarnib
- Data from TIP002 support further clinical development of tipifarnib in PTCL, especially the rare AITL subtype that has a high unmet need with few approved therapies