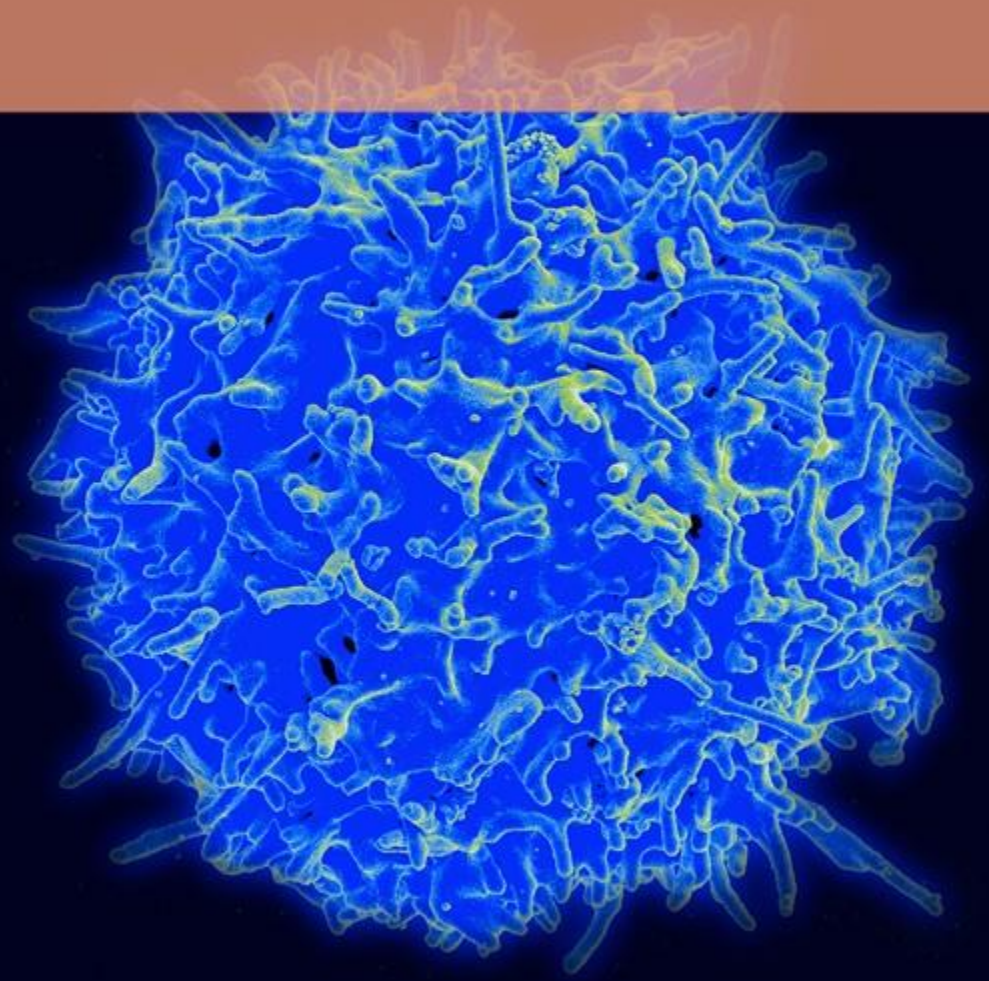
Yale SCHOOL OF MEDICINE

Tipifarnib

…old drug, repurposed



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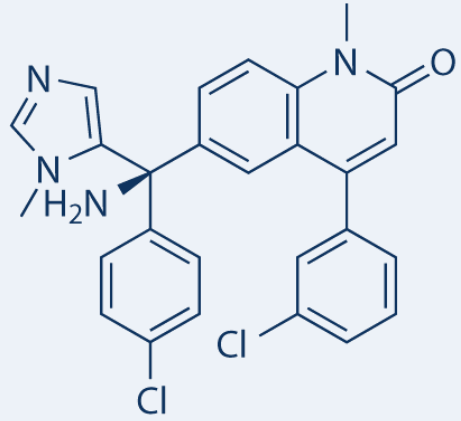
Tipifarnib- old drug, *repurposed*..

- Tipifarnib is an oral farnesyltransferase (Ftase) inhibitor
- FTase is an enzyme important for the maturation of a certain number of proteins, including protooncogenes, such as Ras, Rho-B [20–23], Rac, Rheb, and also nuclear lamins and centromeric proteins
- These proteins are synthesized in the cytoplasm as precursor proteins that require additional posttranslational modifications which are accomplished by a prenylation reaction involving the attachment of a 15-carbon farnesyl group to the C-terminal cysteine residue, mediated by an enzyme, the FTase.
- Based on the assumption that interruption of prenylation may prevent cellular events that depend on the function of those substrates, several classes of FTase inhibitors (FTI) have been designed
- Tipifarnib has been administered to > 5,000 patients
- 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



Phase II trial and prediction of response of single agent tipifarnib in patients with relapsed/refractory mantle cell lymphoma: a Groupe d'Etude des Lymphomes de l'Adulte trial

- 11 pts treated, one CR
- Biomarker predictive of response

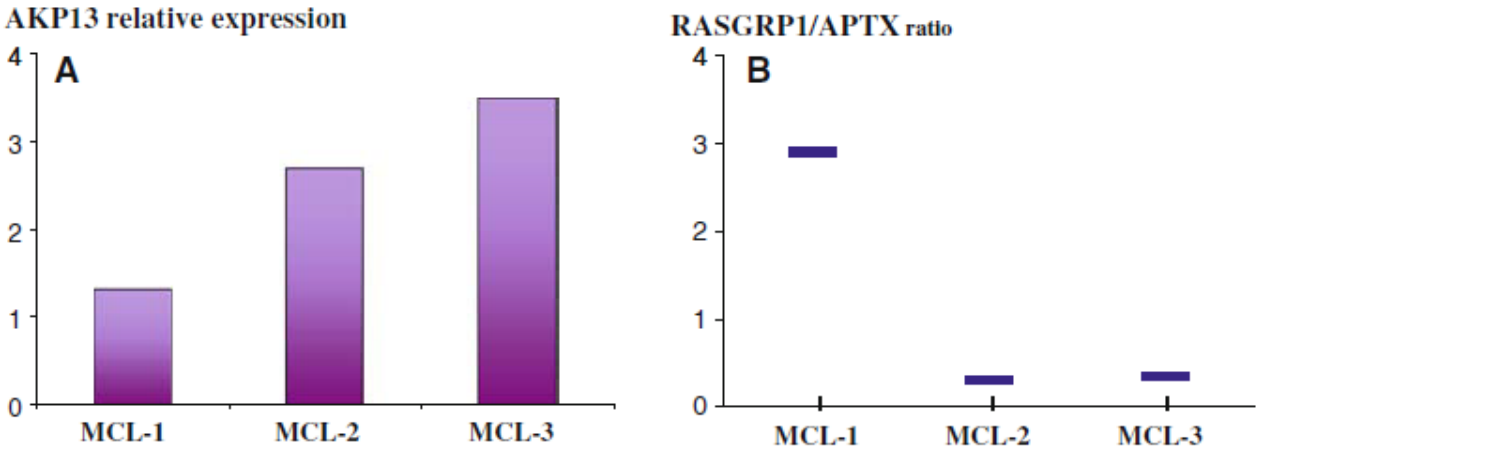


Fig. 3 Response prediction to tipifarnib. Prediction of response was retrospectively evaluated in the initial tumor biopsy by the analysis of the *AKAP13* expression level (**a**) and the *RASGRP1/APTX* gene expression ratio (**b**). The *RASGRP1/APTX* gene expression ratio was higher in the responder while the *AKAP13* expression was higher in the non-responders. This corresponds to the expected result to the response prediction to tipifarnib

Rolland et al, Can Chem Pharm 2010

T-cell Lymphomas: *Tipifarnib*

Tipifarnib Phase 2 Trial in Lymphoma

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*

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

Multi-institutional phase 2 study of tipifarnib in relapsed and refractory lymphomas

- 93 pts in safety analysis
- Dose 300 mg bid x 21 days in 28- day cycle
- 38% required dose reduction
- 14 pts had dose escalation to 400 and one to 600 BID

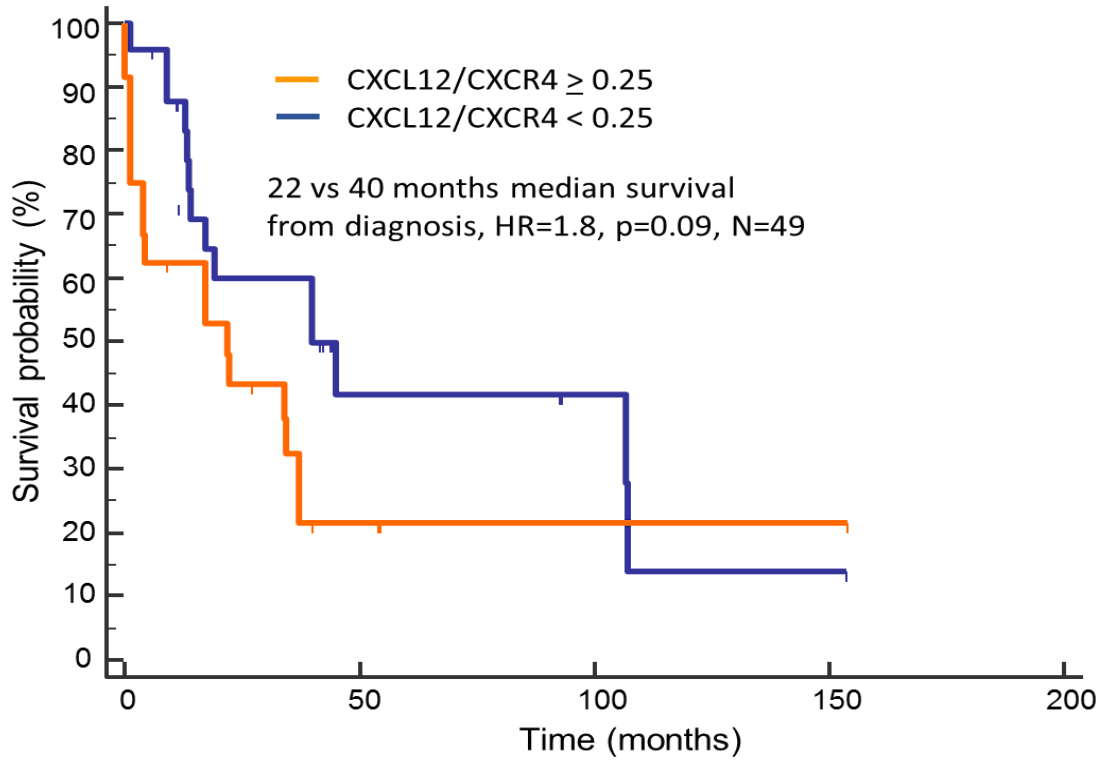
Witzig et al, Blood 2011

Table 3. Grade 3 or 4 toxicity (adverse events considered at least possibly related to tipifarnib) was observed in 58% (54 of 93) of patients

Toxicity	Grade 3	Grade 4	Total, no. (%)
General			
Fatigue	9	0	9 (10)
Hypotension	0	1	1 (1)
Prolonged PT	1	0	1 (1)
Dehydration	2	0	2 (2)
Hematologic			
Anemia	8	2	10 (11)
Neutropenia	7	27	34 (37)
Thrombocytopenia	13	17	30 (32)
Infection			
Febrile neutropenia	2	2	4 (4)
Bacteremia	1	1	2 (2)
Pneumonia	1	0	1 (1)
Respiratory tract	0	1	1 (1)
Wound/soft tissue	2	0	2 (2)
Sinus	1	0	1 (1)
Metabolic			
Hypokalemia	1	0	1 (1)
Gastrointestinal			
Diarrhea	1	0	1 (1)
Pulmonary			
Dyspnea	1	0	1 (1)
Pneumonitis	1	0	1 (1)

Tipifarnib inhibition of CXCL12

- **Key characteristics of CXCL12**
  - Expressed primarily by immune cells, endothelial cells and stromal fibroblasts that constitute 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



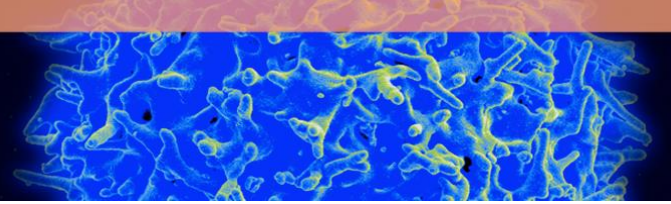
Trend for poor prognosis with high CXCL12 expression (adjusted to CXCR4) in AITL and PTCL NOS pts

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

Tipifarnib KO-TIP-002 Trial

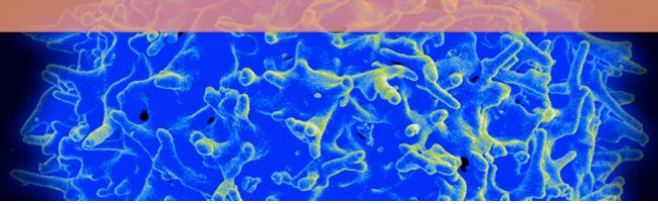
- Multi-center phase 2 single agent in relapsed/refractory T-cell NHL
- 8 PTCL subtypes were allowed to enroll: ALCL- ALK positive or ALK negative, AITL, PTCL – NOS, Enteropathy-associated T-cell lymphoma, Extranodal natural killer (NK) T-cell lymphoma, nasal type, Hepatosplenic T-cell lymphoma,, Subcutaneous panniculitis-like T-cell lymphoma
- 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



Tipifarnib Drug Administration

- 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)

***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

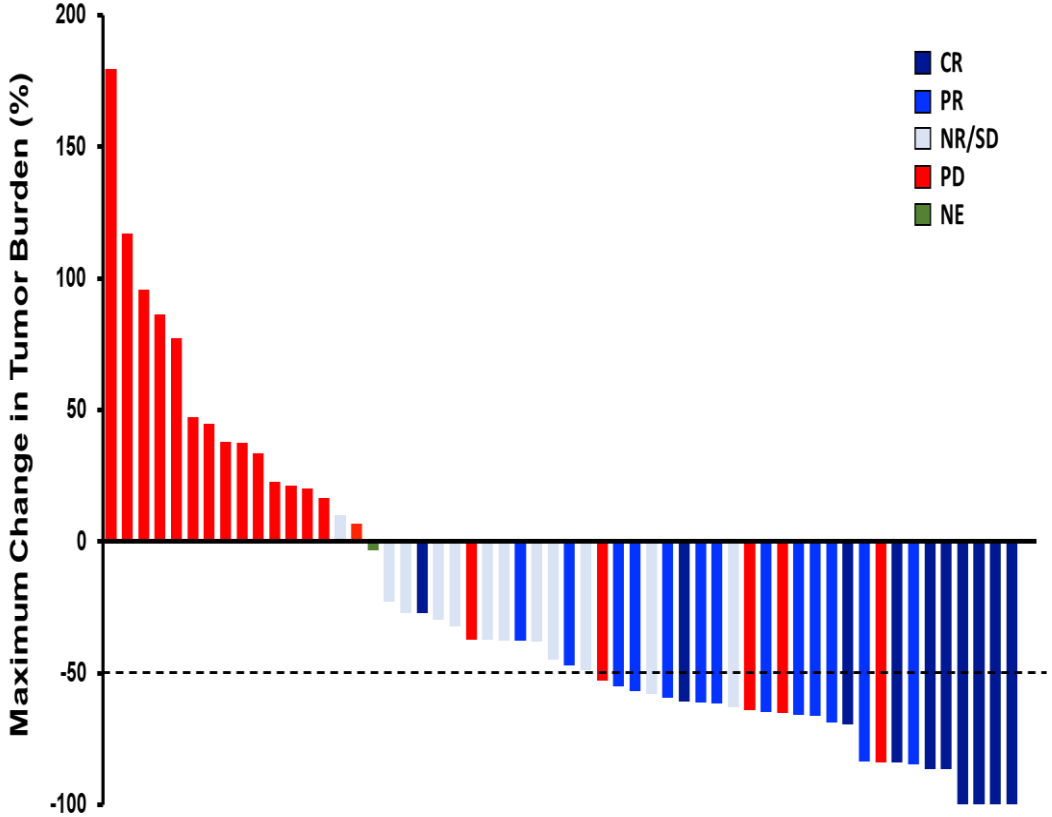
Cohort	PTCL-NOS*, N=24 % (n)	AITL, N = 32 % (n)	Total**, N = 58 % (n)
Primary: Overall Response CR + PR Rate	21 (5)	56 (18)	40 (23)
Complete Response	4 (1)	28 (9)	17 (10)
Partial Response	17 (4)	28 (9)	22 (13)
Stable Disease	38 (9)	9 (3)	21 (12)
Progressive Disease	38 (9)	34 (11)	38 (22)
Non-Evaluable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

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

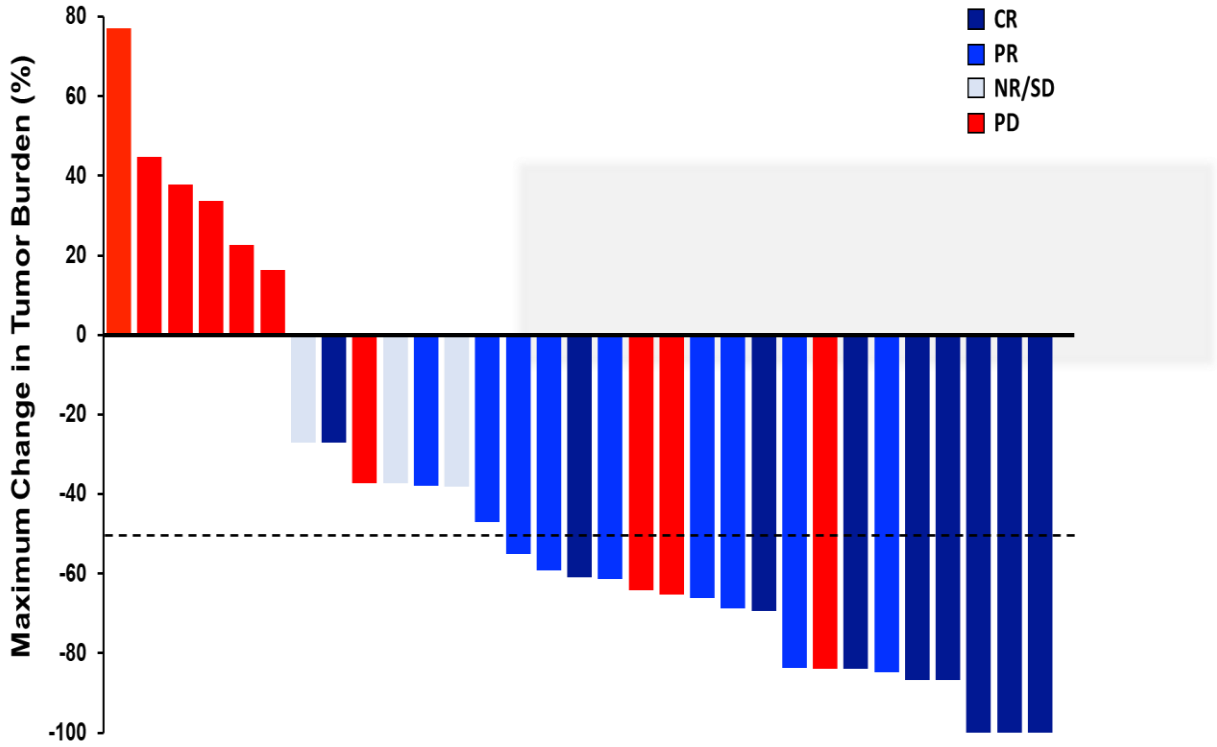
Patients still on drug (compassionate use)
AITL: 2 CR, 19 and 32 months
PTCL-NOS: 1 CR, 40 months

Reduction in Tumor Burden with Tipifarnib Treatment

Greatest Percent Change in SPD* with Best Response (N=56)

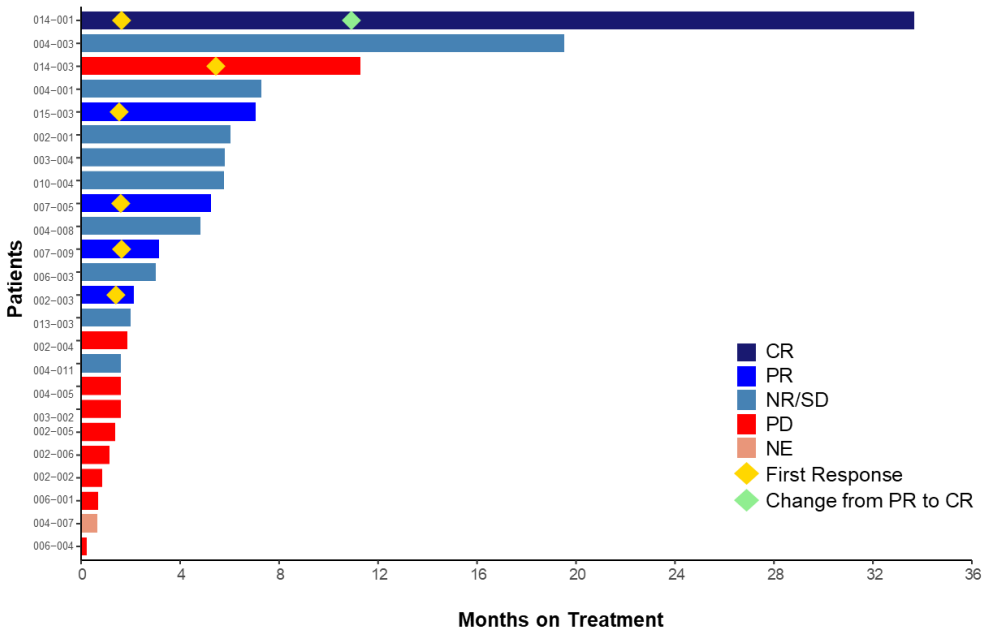


Greatest Percent Change in SPD* with Best Response in AITL (N=31)

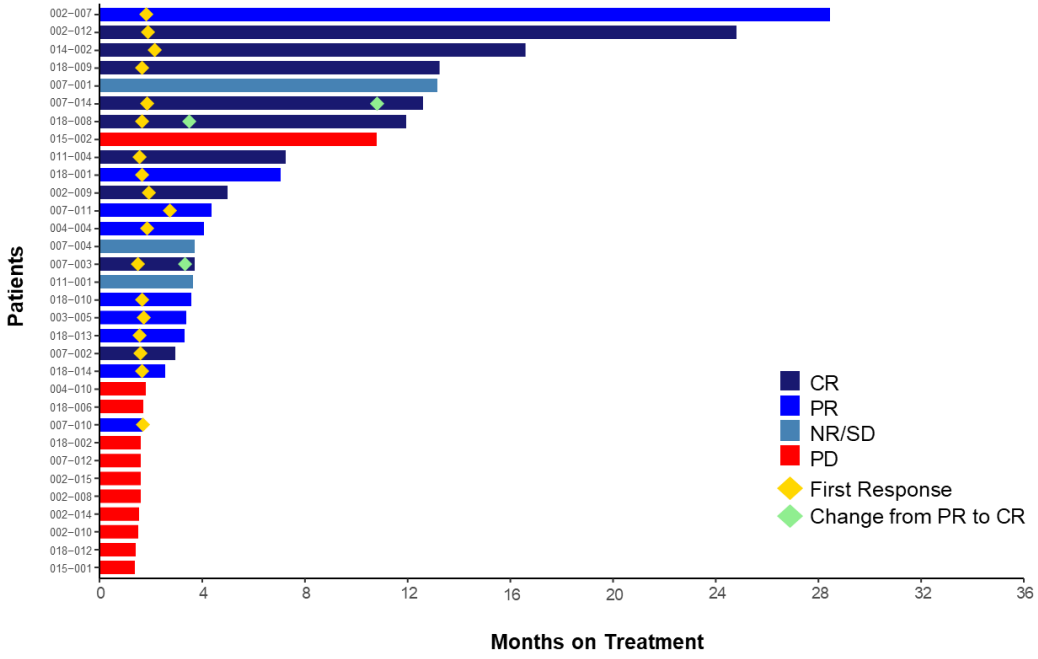


T-cell Lymphomas: *Tipifarnib*

Time to best response

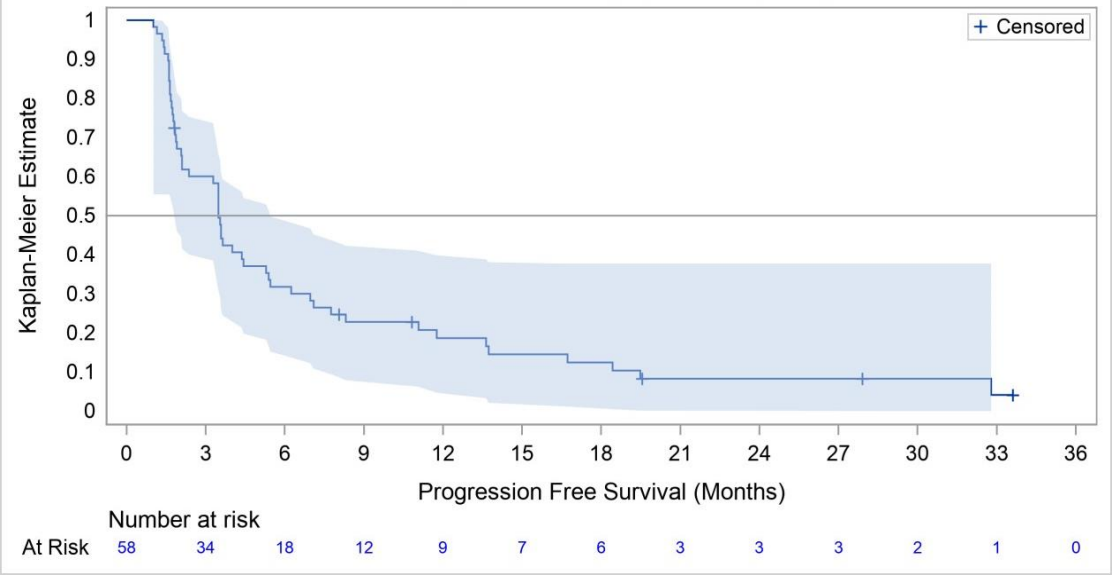


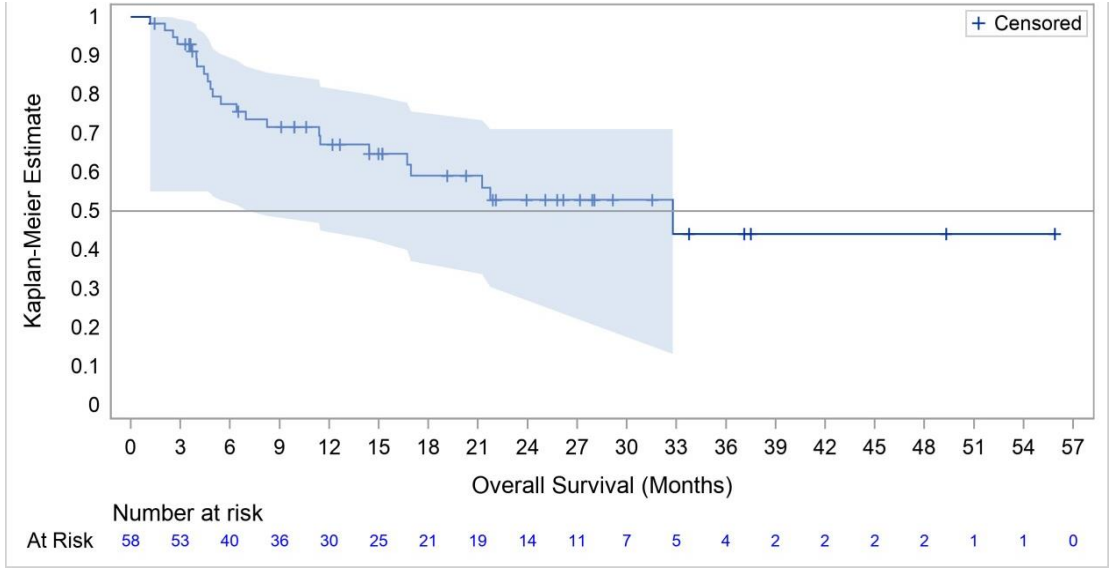
PTCL



AITL

T-cell Lymphomas: *Tipifarnib*





Safety Analysis

- 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)

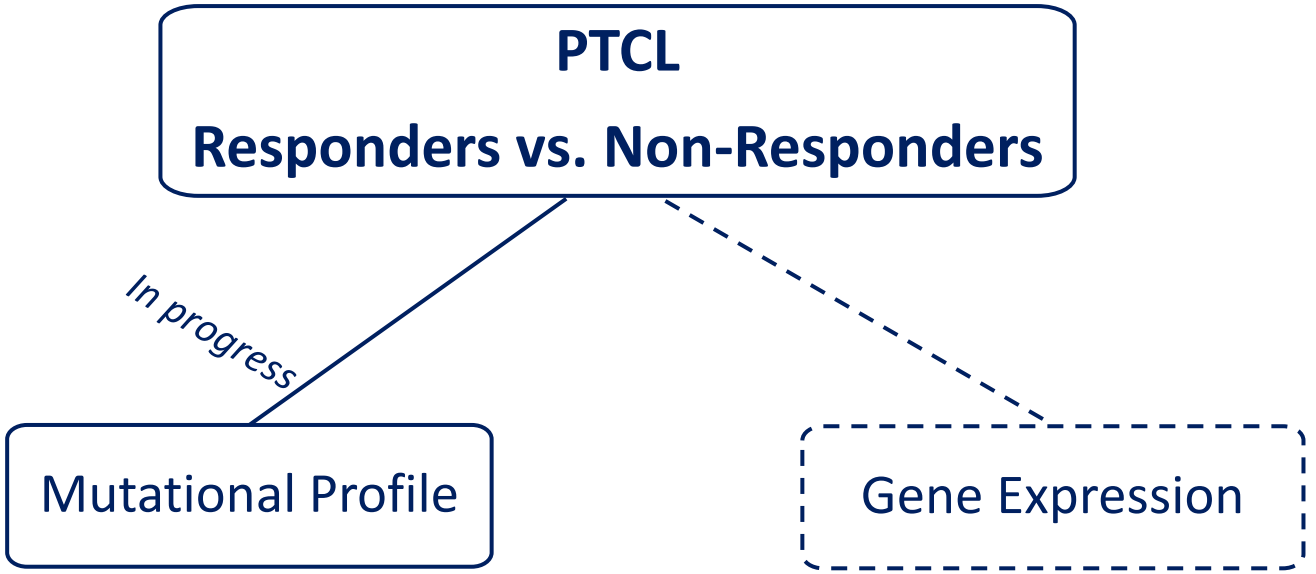
TEAE: treatment emergent adverse event

*Safety evaluable patients N=65

Version 19.0 of MedDRA was used to code AE

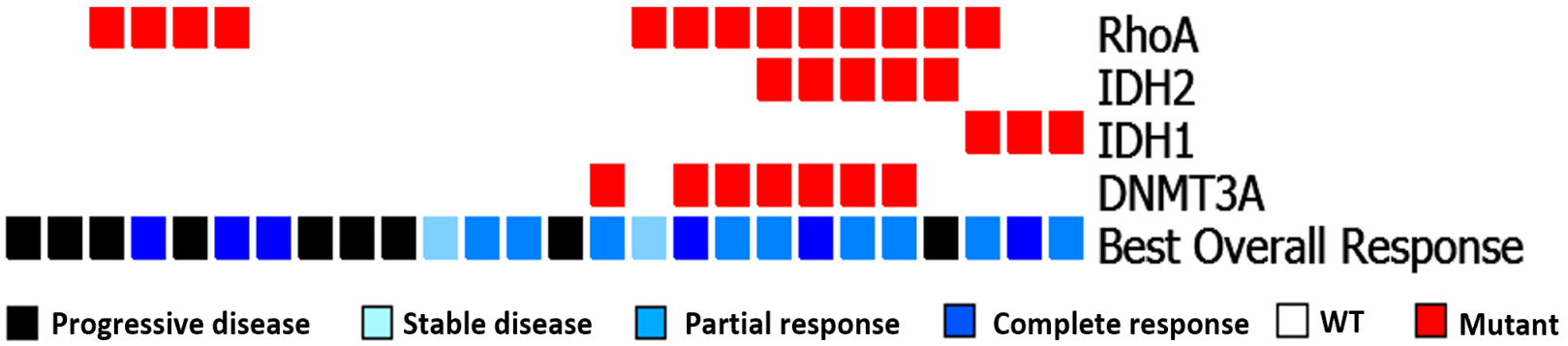
TIP002: Biomarkers of Response to Tipifarnib

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



T-cell Lymphomas: *Tipifarnib*

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*

High activity of tipifarnib in AITL with KIR3DL2 mutations

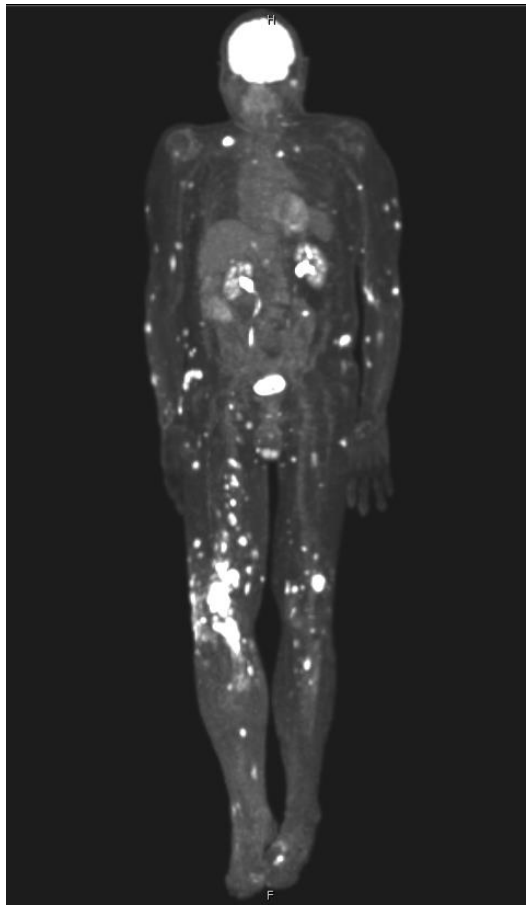
- AITL expresses high levels of CXCL12 and is sensitive to tipifarnib.
- ~50% of AITL carry mutations of KIR3DL2 and are highly sensitive to tipifarnib (50% CR rate).
- High Allele Frequency of KIR3DL2 mutation predicted complete response to tipifarnib treatment (ROC AUC=0.94, p<0.0001)..

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

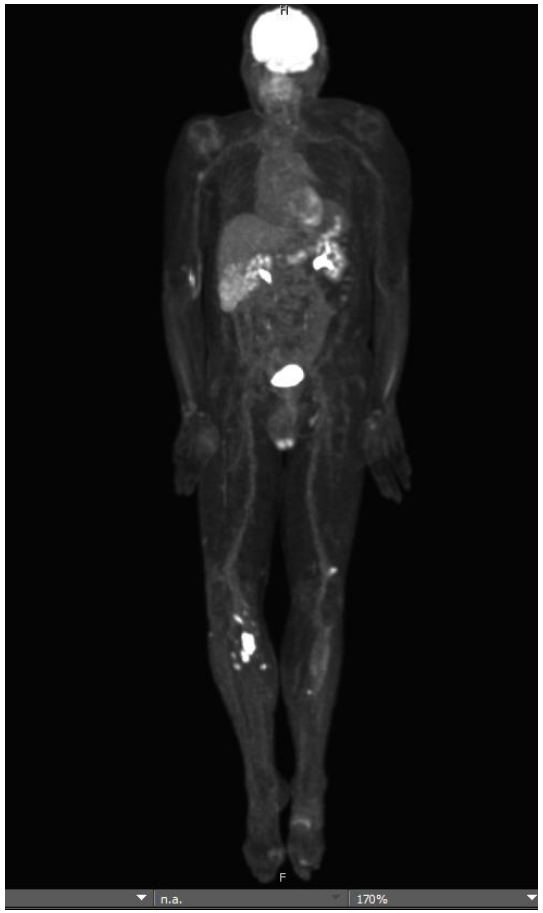
	KIR3DL2 Mutant	KIR3DL2 Wild Type
N	8	8
Overall Best Response		
Complete Response (CR)	4	-
Partial Response (PR)	2	2
Stable Disease (SD)	2	-
Progressive Disease (PD)	-	6
Not evaluable (NE)	-	-
Overall Response Rate (CR + PR)	**75%**	**25%**
95% CI	35.9 - 95.4	4.6 - 64.1
Clinical Benefit Rate (CR + PR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

Presented at 15-ICML: Gualberto et. al. Abstract 156-P

Tumor reduction in PTCL-NOS patient with tipifarnib



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

Conclusions

- 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.
- **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)