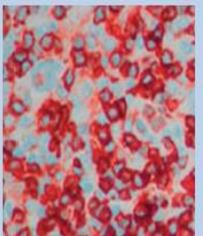





SANTA MARIA ASSUNTA
Policlinico di Sant'Orsola


POLICLINICO DI SANT'ORSOLA

2015... 2018
T-Cell Lymphomas:
we are close to the
finalization



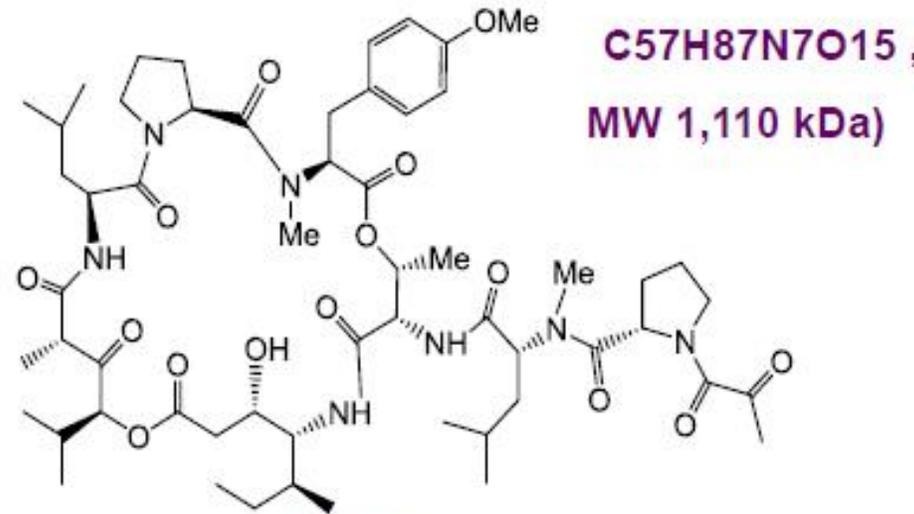
PTCL: new single agents Plitidepsin

Barbara Pro, MD
Northwestern University

Plitidepsin



Aplidium albicans



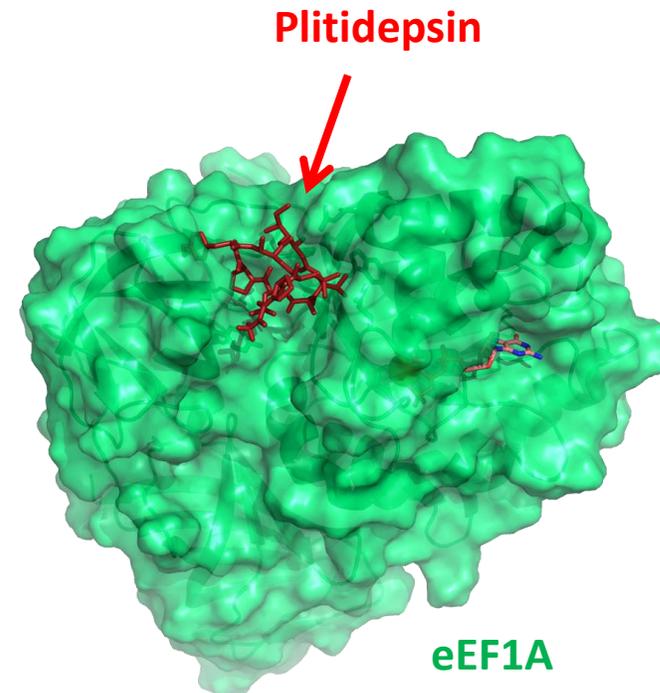
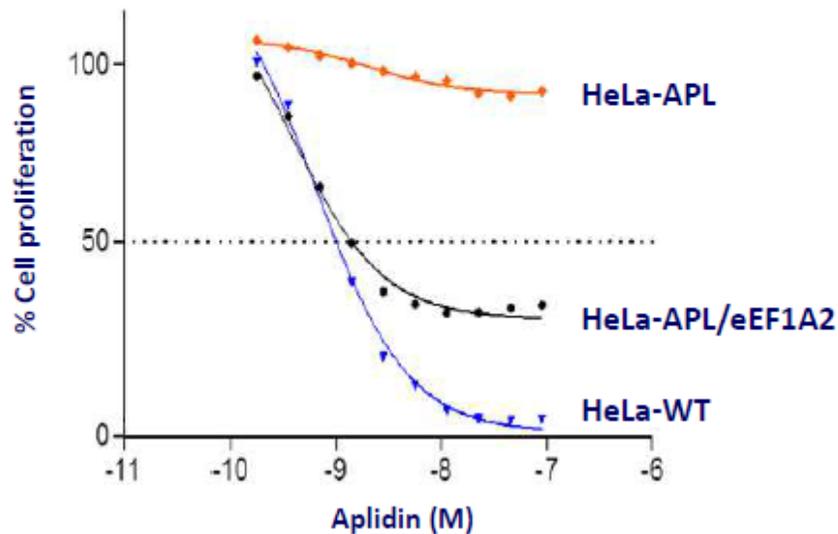
Plitidepsin

- ✓ Cyclic depsipeptide isolated from the marine tunicate *Aplidium albicans*
- ✓ Produced by well-established synthetic process
- ✓ FDA approved starting materials

Demonstrated activity against several human malignant cell lines including leukemia and lymphoma

Plitidepsin target

eEF1 α is the potential target of Aplidin



- Proto-oncogene over-expressed in many tumor types
- Aplidin resistant cells have low levels of expression of eEF1 α
- Re-introduction of eEF1 α sensitizes the resistant cells to plitidepsin treatment

Non-canonical functions of eEF1 α

- ✓ Proto-oncogene over-expressed in many tumor types
- ✓ Reorganization of the actin cytoskeleton
- ✓ Favors cell migration and invasion
- ✓ Target mis-folded proteins to the proteasome
- ✓ Regulation of oxidative stress
- ✓ Inhibition of apoptosis

Plitidepsin

- Currently over **1000 patients** have been treated
- **Activity:**
 - Antitumor activity in phase I/II clinical trials in hematological diseases; **Peripheral T-Cell Lymphoma and Multiple Myeloma**
- **Safety:**
 - **Myelosuppression is very uncommon** and generally mild.
 - Main DLTs: **myalgia, fatigue, CPK and transaminase elevations, transient and reversible**
- **Schedules:** two short infusion schedules selected for further development:
 - Weekly: RD = 3.2 mg/m² days 1, 8, 15 q4wk over 1-hr



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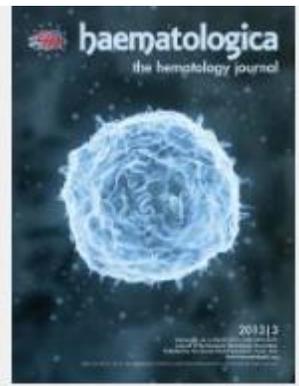
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Multicenter Phase II Study Of Plitidepsin In Patients With Relapsed/Refractory Non-Hodgkin's Lymphoma

Vincent Ribrag, Dolores Caballero, Christophe Fermé, Emanuele Zucca, Reyes Arranz, Javier Briones, Christian Gisselbrecht, Gilles Salles, Alessandro M. Gianni, Henry Gomez, Carmen Kahatt, Claudia Corrado, Sergio Szyldergemajn, Sonia Extremera, Bernardo de Miguel, Martin Cullell-Young, Franco Cavalli

Haematologica March 2013 98: 357-363; **Doi:**10.3324/haematol.2012.069757

Plilidepsin-Phase II Study



- Patients divided in two cohorts
 - Non-cutaneous PTCL
 - Other lymphomas
- Dosing: plitidepsin 3.2 mg/m² (1-hour intravenous infusion) on days 1, 8, and 15 of a 28-day cycle
- Patients with SD or response could continue to receive treatment until PD or unacceptable toxicity
- Response assessed every 2 cycles



Plilidepsin-Phase II Study Efficacy

Best response	PTCL (n=34)	Other (n=33)
ORR	20.7 (29)	-
CR/Cru*	2 (5.9)	-
PR**	4 (11.4)	3 (11)
SD	6 (17.6)	9 (33)
NE	5(14.7)	3 (9.1)
PD	17 (50)	24(72)

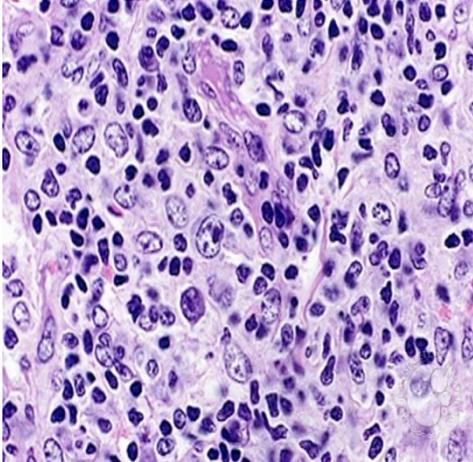
*2 CR in AITL, both patients had failed ABMT

** 1 PR in AITL, 3PR in PTCL-NOS

Plitidepsin-related adverse events (at least 5% of patients)

Adverse event	All patients (n=64)*							
	Grade 1/2		Grade 3		Grade 4		Total	
	N.	%	N.	%	N.	%	N.	%
Plitidepsin-related adverse events								
Constipation	4	6	4	6
Diarrhea	5	8	5	8
Fatigue	15	23	.	.	1	2	16	25
Muscle cramps	4	6	4	6
Muscle weakness	4	6	1	2	1	2	6	9
Myalgia	13	20	1	2	.	.	14	22
Nausea	22	34	22	34
Pyrexia	5	8	5	8
Vomiting	9	14	9	14
Hematologic abnormalities								
Anemia	51	80	10	16	.	.	61	95
Leukopenia	17	27	2	3	2	3	21	33
Lymphopenia	24	38	17	27	4	6	45	71
Neutropenia	9	14	4	6	3	5	16	25
Thrombocytopenia	24	38	4	6	6	9	34	53
Biochemical abnormalities								
ALT increased	38	60	14	22	.	.	52	83
Amylase increased	3	6	1	2	.	.	4	8
AP increased	27	43	2	3	.	.	29	46
AST increased	42	67	7	11	.	.	49	78
CPK increased	9	15	1	2	4	7	14	23
Creatinine increased	18	28	1	2	.	.	19	30
Total bilirubin increased	19	31	1	2	.	.	20	33

* Patients evaluable for safety. Data shown are number and percentage of patients (based on patients with available data). Only laboratory abnormalities reaching grade 3 or 4 are shown. PTCL: peripheral T-cell lymphoma; ALT: alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransferase; CPK: creatine phosphokinase.



APL-B-021-13
PHASE II STUDY OF PLITIDEPSIN IN
PATIENTS WITH RELAPSED OR
REFRACTORY ANGIOIMMUNOBLASTIC
T-CELL LYMPHOMA

Study design

- **Primary objective:** To evaluate the efficacy of plitidepsin on the basis of overall response rate (ORR) in patients with relapsing/refractory angioimmunoblastic T-cell lymphoma (AITL).
- **Secondary endpoints:**
 - Other secondary endpoints of efficacy:
 - Duration of response.
 - Progression-free survival, PFS at 6/12 months.
 - Inpatient TTP/PFS.
 - Overall survival, OS at 6/12 months
 - Safety profile of plitidepsin in this patient population.
 - Pharmacokinetics (PK) of plitidepsin.
 - **To identify biomarkers that may be clinical endpoint surrogates for future plitidepsin studies or that may be predictive of plitidepsin activity.**

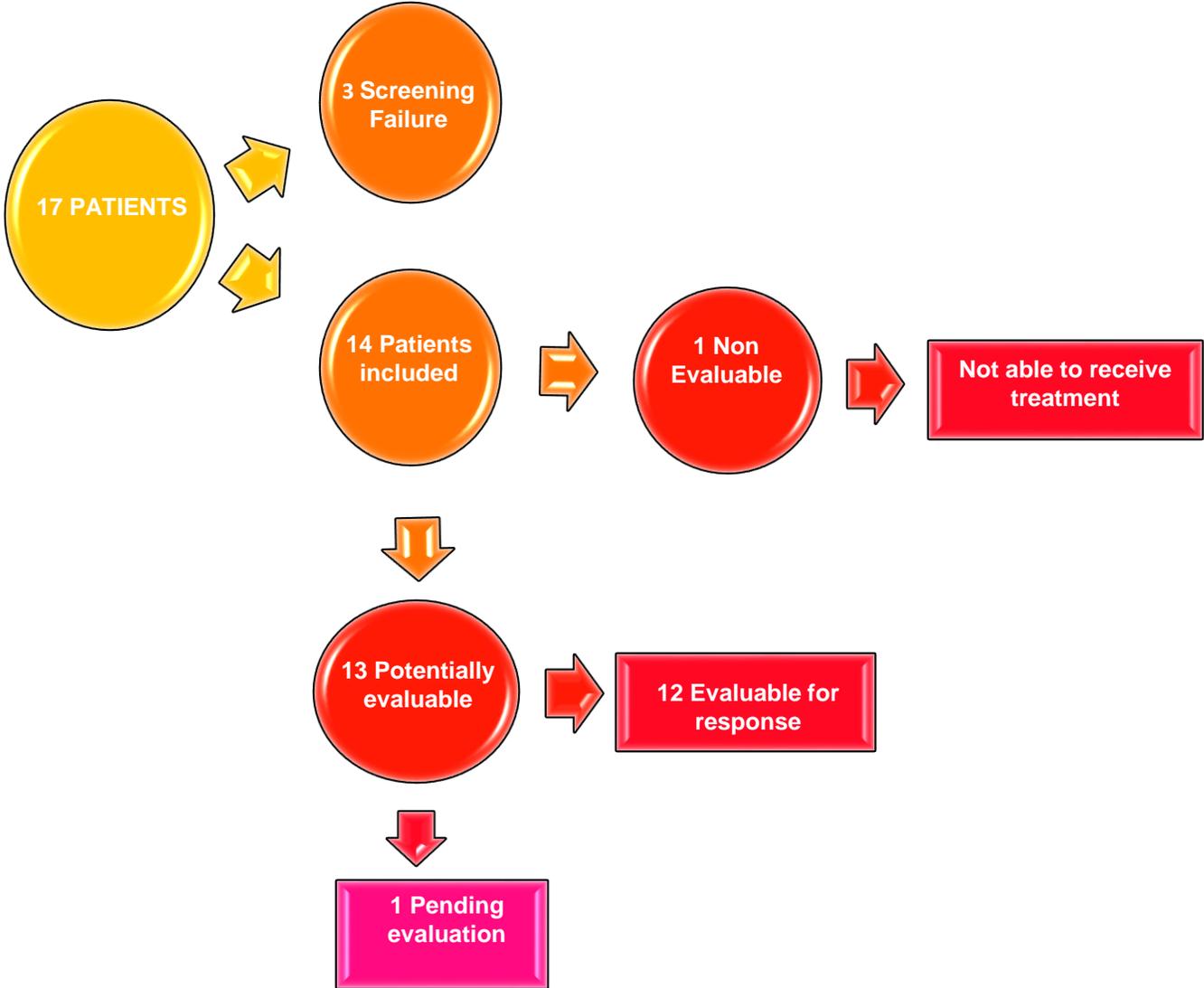
Statistical Methods

- The primary endpoint for this study is ORR according to the Lugano classification 2014 response criteria per independent central review
- **Two futility analyses of the primary endpoint** when approximately 25% and 50% of eligible patients have been treated (i.e., 15 and 30 patients, respectively).
 - For the first analysis ≥ 3 responders out of 15 patients are required.
 - For second analysis ≥ 8 out of 30 patients are required.
 - If these objectives are not met recruitment might be stopped at the time of the first or second futility analysis, respectively.
 - Otherwise, accrual will continue to a total of 60 patients.
 - If there are 19 or more responders over the total of 60 patients, the efficacy of plitidepsin will be considered as clinically relevant in AITL patients.
 - Active recruitment will not be halted while the analysis is being carried out.

Central Pathological Review-Biomarker Analysis

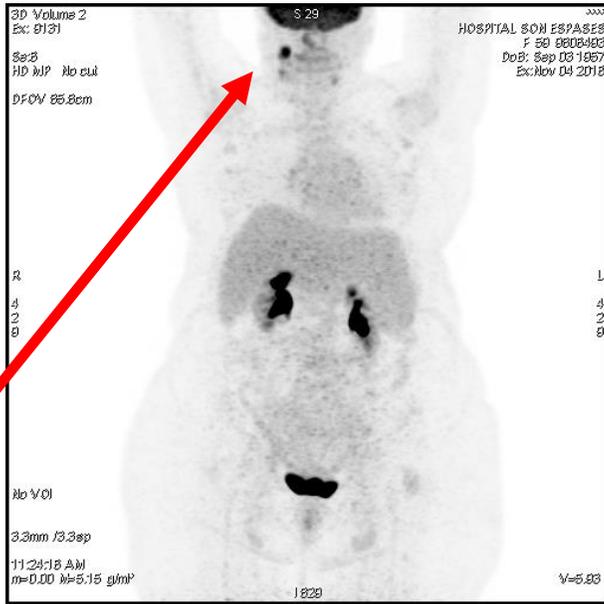
- The pathologists responsible for the central pathological review will be responsible for:
 - a) Confirming patient eligibility on the basis of investigative site pathology reports provided during screening,
 - b) Analyzing tumor biopsies (initial diagnosis and/or relapses) to ensure consistency of the AITL diagnosis.
 - c) Analyzing blood samples to identify plasma biomarkers.
- The assessment of potential predictive factors
 - alterations in DNA and RNA, including DNA mutational status, RNA expression levels and miRNA expression, for common genetic lesions affecting the AITL clone
 - alteration in tumor tissue biomarkers including (but not limited to) assessment of pathways and mechanisms of action of plitidepsin, mainly status at the protein expression level; and
 - peripheral blood analyses, to identify plasma biomarkers including (but not limited to) cancer-related mutations and to extract DNA.

UPDATED STUDY STATUS



Case

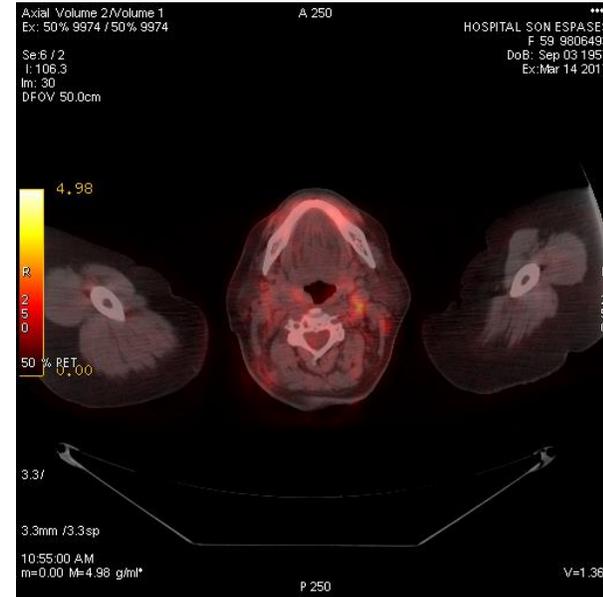
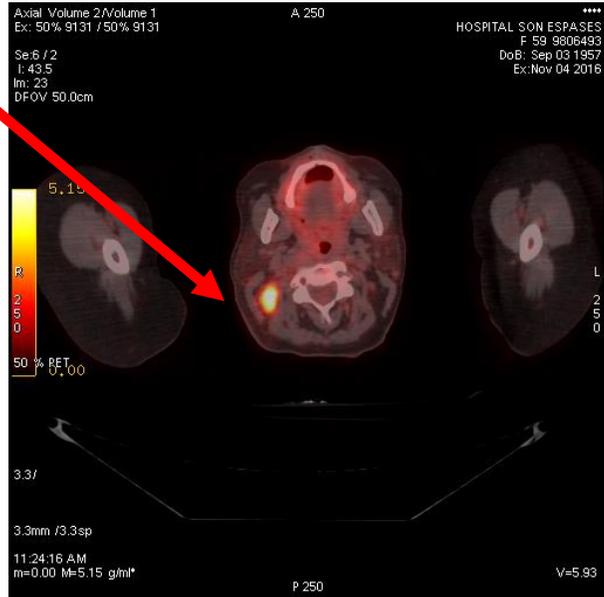
- 59 years old woman with diagnosis of angioimmunoblastic lymphoma stage IVA refractory to 2 prior lines
- She began treatment with plitidepsin 3 weekly doses every 4 weeks
 - After the first cycle she had resolution of laterocervical nodes
 - After 3 cycles a PET/CT showed that the original lesion resolved but there was an increase in FDG uptake without increasing in size of multiple other nodes



Original lesions



The original lesion disappeared but there is an increase in FDG uptake without increasing the size of multiple other nodes that were not hypermetabolic before therapy.



Conclusions

- Plitidepsin has moderate single-agent activity with an **acceptable safety profile** in relapsed/refractory non-cutaneous PTCL patients.
- **Hematologic toxicity was not clinically relevant** nor dose limiting in a heavily pretreated cohort, making plitidepsin an ideal agent to treat patients with limited bone marrow reserve and/or to combine it with other active drugs.
- The ongoing clinical trial will hopefully elucidate the underlying molecular mechanisms responsible for the observed clinical selectivity in patients with AITL.



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CENTRO NAZIONALE DI RIFERIMENTO
PER LA DIAGNOSI E LA TERAPIA
DEI TUMORI EMATOLOGICI

2015... 2018
T-Cell Lymphomas:
we are close to the
finalization

