Plitidepsin is active in peripheral T-cell lymphoma: a subset analysis from an ongoing multicenter phase II trial

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A B S T R A C T

Background. Peripheral T-cell lymphomas (PTCL) represent a small (<10%) yet a particularly aggressive subset of NHL. Up to 75% of those patients (pts) eventually become relapsed/refractory, with no effective options available. Thus, a prospective open label, multicenter phase II study to evaluate the activity of plitidepsin (Aplidin®) in adult pts with relapsed/refractory aggressive lymphomas was planned and is currently ongoing. We report the preliminary results from a cohort of non-cutaneous PTCL.

Patients and methods. As of December 2008, 19 pts were treated with plitidepsin 3.2 mg/m^2 i.v. infusion over a 1-h on days 1, 8 and 15 q4wk. Sixteen pts have been evaluated, one is too early and two were non-evaluable as *per* protocol criteria: one had a hypersensitivity reaction and one had cutaneous involvement exclusively. Pts had a median of 3 (1-6) previous regimens, including 4 pts (33%) with prior autologous transplantation. Lymphoma histology: 11 PTCL-nos, 3 anaplastic large-cell, 3 angioimmunoblastic and 2 NK/T nasal type. Ten pts were male, median age was 56 y (35-74), with performance status 0 in 6 pts, 1 in 5 pts and 2 in 3 pts.

Results. Two CR (1 unconfirmed) and 2 PR were observed for a 25% objective response rate (95% CI: 11%-70%). Median duration of response was 4 months (range: 1+ - 12+). Median overall survival was 11 months (range 1+-24+). Plitidepsin was tolerable in this heavily pre-treated population, particularly with low hematologic toxicity. Of 2 cases of grade (G) 4 neutropenia, 1 was already present at baseline and only 1 pt developed G3 thrombocytopenia during treatment. Transient and reversible G3 ALT/AST elevations occurred in 7 patients. Clinical toxicities mainly consisted of mild to moderate muscular weakness, myalgia and cramps, plus G1-2 fatigue and nausea in 1/3 of the patients.

Conclusion. Plitidepsin (Aplidin®) shows promising activity and an acceptable safety profile in this difficult-to-treat subset of patients. Remarkably, no significant hematologic toxicity was seen in this heavily pretreated cohort. To confirm these preliminary data an expansion of the cohort is currently ongoing. Updated

Background

- Non-cutaneous Peripheral T-cell lymphomas (PTCL) represent a small (<10%) yet a particularly aggressive subset of NHL. Up to 75% of those patients (pts) eventually become relapsed/refractory. No effective options are currently available.
- Aplidin® is a new compound of marine origin in Phase II stage of clinical development. Its mechanism of action is not yet fully understood, although it may involved reactive oxygen species induction, JNK pathway activation as well as downregulation of VEGF and VEGF-R1 expression. Potent anti-tumour activity (in the nanomolar range IC50s) against a wide range of neoplasms has been shown both *in vitro* and *in vivo* in preclinical models, particularly against T-cell lymphoma cell lines.
- In previous phase I trials conducted with Aplidin®, preliminary activity has been observed in non-Hodgkin lymphoma (NHL) patients.

Objectives

- **Primary**
  - To assess the anti-tumour activity of Aplidin® given as a 1-hour weekly IV infusion, in patients with aggressive non-cutaneous peripheral T-cell Lymphoma (PTCL), relapsing or refractory to a prior therapy.
- **Secondary**
  - To further investigate the safety profile of Aplidin® given as 1-hour weekly IV infusion in this patient population.
  - Pharmacogenomic analysis of putative response and/or resistance predictive factors in this patient population
- **Treatment**
  - Aplidin® given 3.2 mg/m^2 on days 1,8 & 15 q4wk as a 1-hour IV infusion

Eligibility

- Written informed consent, Age ≥ 18 years, PS(ECOG) ≤ 2
- Histologically confirmed relapsed/refractory aggressive PTCL, including the following:
  1. Adult T-cell lymphoma/leukemia (HTLV1)
  2. Extranodal NK/T-cell lymphoma, nasal type
  3. Enteropathy-type T-cell lymphoma
  4. Hepatosplenic gamma-delta T-cell lymphoma
  5. Subcutaneous panniculitis-like T-cell lymphoma
  6. Peripheral T-cell lymphoma, not otherwise characterized
  7. Angioimmunoblastic T-cell lymphoma (AILT)
  8. ALK- or Post-transplant refractory/relapsed ALK+ Anaplastic large-cell lymphoma (ALCL), T/null cell, primary systemic type
- Measurable disease (IWG criteria)
- Adequate renal, hepatic, and bone marrow function
  - Lower hematological values due to bone marrow infiltration could be accepted.
- Adequate cardiac function (LVEF within normal limits).
- Up to 3 previous lines of systemic biological agents or chemotherapies. (Bone marrow or stem cell transplantation as consolidation therapy is understood as one line of chemotherapy).

Study design

- This is a multicentre, open-label, single arm, exploratory Phase II trial.
- Forty nine patients with agressive lymphomas were enrolled.
- A prospective open-label, multicenter phase II study to evaluate the activity of plitidepsin (Aplidin®) was conducted in adult pts with relapsed/refractory aggressive NHL (Both B and T-cell lineage).
- After a preliminary efficacy analysis on 41 evaluable patients as of March 2008 shown that clinical activity was restricted almost exclusively to PTCL patients, the protocol was subsequent amended and only Non-cutaneous PTCL relapsed/refractory patients are allowed to participate in a currently ongoing expansion cohort planned to include 28 evaluable patients.
- We report here the ongoing (as December 2008) results exclusively on the non-cutaneous PTCL cohort of patients:

Patient Characteristics

	N	%
Patients with non-cutaneous-PTCL	**19**	**100**
Age		
Median (years)	57	
Range(years)	35-74	
Gender		
Male	12	71
Female	5	29
Race		
Caucasian	**15**	**88**
Asian	**2**	**12**
PS (ECOG)		
0	7	41
1	6	35
2	4	24

Disease Characteristics N=19

Histology subtype	N (%)	Evaluable
ALCL (systemic type)	3 (16)	3
AILT	3 (16)	2
Extranodal NK/T-cell	2 (10)	2
PTCL nos	11 (58)	9
Total	***19 (100)***	16

Bone marrow involvement (N=15)-	3 (16%)

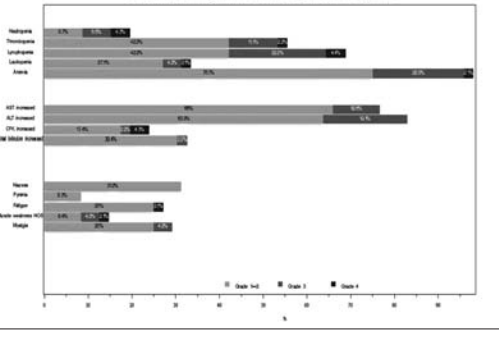
Abbreviations: ALCL: Anaplastic Large Cell Lymphoma; AILT: Angioimmunoblastic type; PTCL nos: Peripheral T-cell Lymphoma not otherwise specified

Prior Treatment

Number of prior lines	N	%
Median (range)	3(1-6)	
<3	8	47
>= 3	9	53
Prior HDCT & SCT	6	35
Time since last therapy (months)		
Median (range)	3 (1-10)	
Time from diagnosis to therapy (years)		
Median (range)	1,4 (0,4-8,3)	

Safety Profile

Drug-related laboratory toxicities and more frequent AEs during treatment



Efficacy		
Response	Patients N=16	%
CR	1	6
CRu	1	6
PR	2	13
OR	4	25
SD*	3	19
PD	9	56
Median TTP in responders (N=4)	6 months	CI95% (3-NR)
Median TTP in all pts (N=13)**	2 months	CI95% (1-3)
OS in responders (N=4)	28 months	CI95% (24-32)
OS in all pts (N=13)	24 months	CI95% (3-32)

•*2 pts are ongoing

•**Ongoing and non-evaluable pts not included

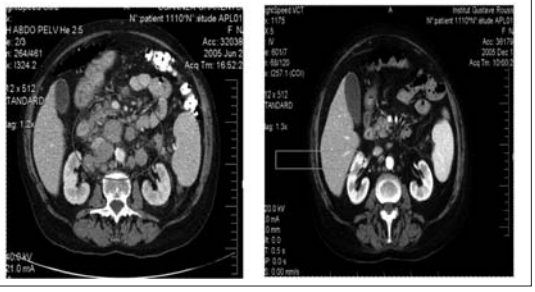
•NR: Not reached

Responders layout

ID	Gender / Age	ECOG/ PS	Histology subtype	# lines	Bulky lesion 25cm	HDCT & SCT	#Cy	EOT reason	Response	TTP (Months)
#1139	M/ 56	1	AILT	3	Yes	Yes	8	Complete	CR	12+ ongoing
#1113	M/ 35	0	PTCL-nos	2	No*	Yes	4	Toxicity	CRu	4
#1110	F/ 65	0	PTCL-nos	3	No	No	6	Complete	PR	8
#1643	M/ 69	0	AILT	2	No	No	3	PD	PR	3

*BM involvement

Dramatic lymph node response in a 65-y old woman with a PTCL-nos after 6 cy of Aplidin®



Conclusions

- Plitidepsin (Aplidin®) shows activity and an acceptable safety profile in relapsed/refractory non-cutaneous PTCL patients. Prolonged disease remissions were observed. Interestingly, 2 out of 2 AILT evaluable patients so far responded to plitidepsin (a particularly difficult-to-treat subset of pts).
- Only 1 patient out of 4 responders progressed while on treatment.
- Remarkably, hematologic toxicity was not clinically relevant nor dose limiting in this heavily pretreated cohort.
- Research is ongoing in order to elucidate the underlying molecular mechanisms responsible for the observed clinical selectivity in PTCL patients.
- Confirmation of this encouraging results in the expansion cohort is currently ongoing.

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