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BACKGROUND

- The outcome of MM patients has improved in the recent years with the introduction of **novel therapeutic agents**. Nevertheless most patients are refractory or relapse after achieving a response. Therefore, the development of new compounds is still needed to **overcome the drug resistance displayed by myelomatous plasma cells**.
- Plitidepsin** is a cyclic depsipeptide isolated from the marine tunicate, Aplidium lbianus with promising antitumor activity.
- This work represents a **comprehensive study** (*in vitro*, *in vivo* and clinical) of its antimyeloma efficacy.

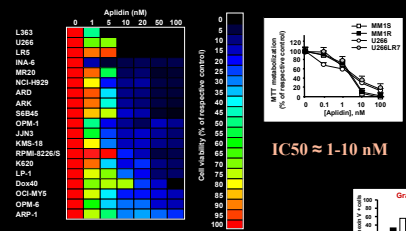
MATERIAL & METHODS

- In vitro* studies were performed in 23 multiple myeloma (MM) cell lines and in cells from 16 MM patients.
- For the *in vivo* analysis a human plasmocytoma model in CB17-SCID mouse was used. Mice were randomized to receive Aplidin® 100 µg/Kg ip x 7 days/week (n=9), Aplidin® 140 µg/Kg ip x 5 days/week (n=7) or vehicle alone (n=9).
- The **clinical** efficacy of Aplidin® in relapsed/refractory patients was evaluated in a Phase II trial. Dosage of Aplidin® was 5 mg/m² every 2 weeks. Dex was added after 3 cycles if PD or after 4 cycles if SD.

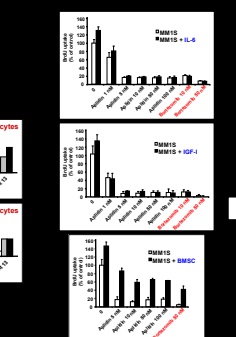
RESULTS

In vitro efficacy

Aplidin® is very effective against MM cell lines



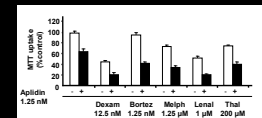
Aplidin® overcomes the proliferative effect of IL-6 and IGF-1 but only partially that of BMSCs



Efficacy against cells from 16 MM patients without toxicity in normal cells

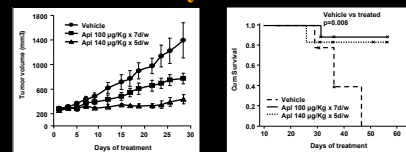
Patient	Previous treatments	% of AA V+ PC	
		Ap 10 nM	Ap 100 nM
1	At diagnosis	100	100
2	At diagnosis	79	100
3	VBCMP/VBAD-ASCT, Bortezomib, TACYDEX	96	99
4	MP, VBAD, Bortezomib	83	97
5	At diagnosis	53	92
6	At diagnosis	69	89
7	VBCMP/VBAD	33	83
8	VBCMP/VBAD-ASCT2	52	81
9	At diagnosis	32	74
10	VBCMP/VBAD-ASCT, High Dex, TACYDEX	44	71
11	VBCMP/VBAD-ASCT, Bortezomib	49	66
12	MP, VBAD	37	61
13	At diagnosis	39	61
14	MP	7	33
15	At diagnosis	0	22
16	At diagnosis	2	18

Aplidin® potentiates the effect of other antimyeloma agents



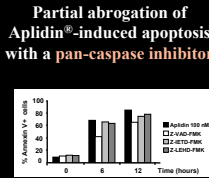
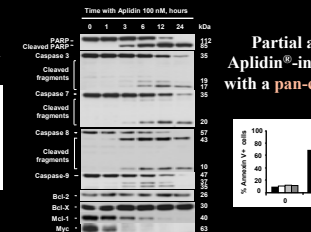
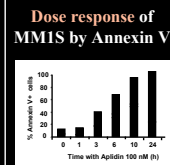
In vivo efficacy

Aplidin® reduces tumor growth and increases survival in a human plasmocytoma (MM1S) in CB17/SCID mice

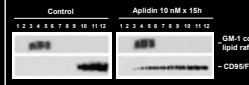


Mechanism of action

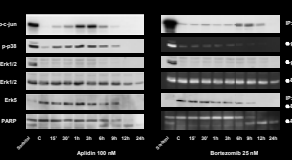
Treatment of MMIS with Aplidin® induce caspase dependent apoptosis



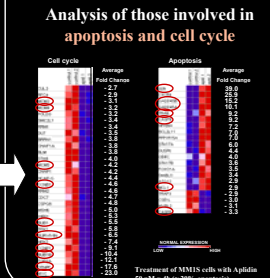
Aplidin® induces CD95/Fas translocation into lipid rafts in MM144 cells



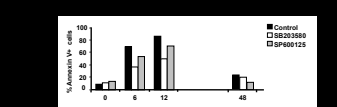
Aplidin®-induced apoptosis is, at least partially, mediated through JNK and p38 activation



Aplidin® induces deregulation of 805 genes by GEP analysis



Partial abrogation of Aplidin®-induced apoptosis with the pretreatment of MMIS cells with a JNK- and a p38 kinase-inhibitor



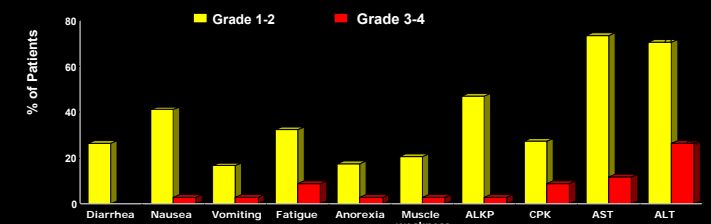
Clinical trial

35 relapsed/refractory MM patients have been included. Median number of previous lines of therapy: 4 (1-9). 12 pts have received Thal-based combinations and 15 pts Bortezomib-based regimens.

Data from 29 evaluable patients for APL alone	RESPONSE	N (%)
• Best Response for APL alone:		
• 2 patients (6.9%) obtained a PR	PR	2 (6.9%)
• 3 patients (10.3%) obtained a MR	MR	4 (13.7%)
• 9 patients (31.0%) obtained a SD		
• Best Response for APL/Dex (5 pts):		
• 1 pt in SD → SD	PR+MR	6 (20.6%)
• 4 pts in PD → 1 pt MR	SD	12 (41.3%)

	APL single agent	APL/ Dex
Overall Median TTP	2.2 mo. (1.5 - 2.5)	2.4 mo. (1.6 - 3.1)
Median TTP in PR/MR	5.4 mo. (1.9 - 7.6)	7.9 mo. (1.9 - 8.6)
Median TTP in SD	2.7 mo. (2.3 - 4.7)	3.1 mo. (2.3 - 4.7)

Toxicity profile



CONCLUSIONS

- Aplidin® is effective both as a **single agent** and **in combination with dexamethasone** in the *in vitro* and *in vivo* settings
- Its activity in relapsed/refractory MM patients is **promising with an acceptable toxicity profile**