RANDOMIZED PHASE III STUDY (ADMYRE) OF PLITIDEPSIN IN COMBINATION WITH DEXAMETHASONE VS. DEXAMETHASONE ALONE IN PATIENTS WITH RELAPSED / REFRACTORY MULTIPLE MYELOMA.

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BACKGROUND 1

Plitidepsin is a synthetic cyclic depsipeptide isolated from the marine tunicate *Aplidium albicans.*

The target is the proto-oncogene eEF1A2, over-expressed in multiple myeloma cells.

Potent anti tumor activity has been shown both in vitro and in vivo in preclinical models, particularly against multiple myeloma and T-cell lymphoma.

In a previous phase II trial of plitidepsin plus dexamethasone (APL-B-014-03) conducted in patients with relapsed and/or refractory multiple myeloma, preliminary activity was demonstrated with an ORR (CR+PR+MR) of 22% and PFS of 4.2 months.

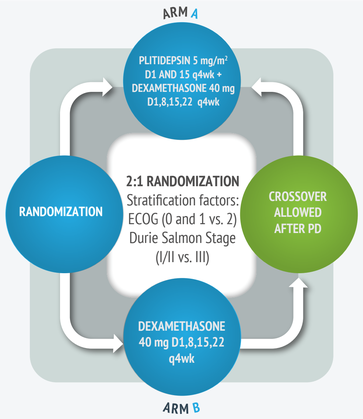
STUDY DESIGN 2

This was a multicenter, open-label randomized trial.

255 patients enrolled: 171 in Arm A , 84 in Arm B. 37 out of these 84 were crossed to Arm A after disease progression.

Sites participation: Europe, USA, Australia, New Zealand, Taiwan, South Korea.

PATIENTS WITH RRMM ≥3-6 PRIOR LINES EXPOSED TO BORTEZOMIB AND LENALIDOMIDE OR THALIDOMIDE

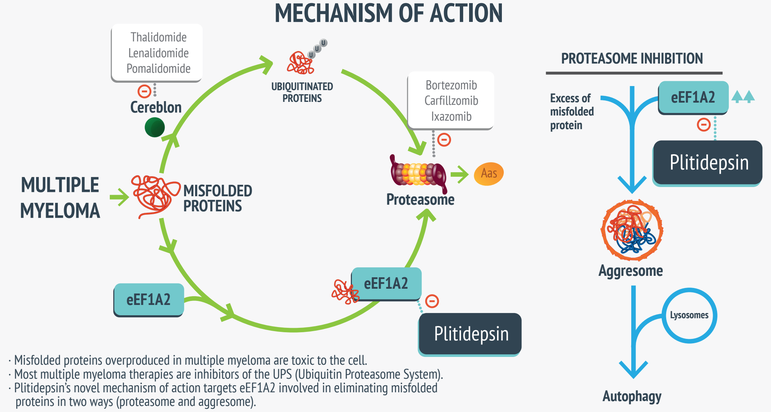


Hematological parameters:
ANC ≥ 1.0 x 10^9/l
Platelet count ≥ 50 x 10^9/l
Hemoglobin ≥ 8.5 g/dL

Biochemical parameters:
AST and ALT ≤ 3 ULN.
Creatinine clearance (CrCl) ≥ 30 ml/minute
CPK ≤ 2.5 x ULN
Albumin ≥ 2.5 g/dL.

Normal left ventricular ejection fraction (LVEF) by ECHO or MUGA.

MECHANISM OF ACTION



· Misfolded proteins overproduced in multiple myeloma are toxic to the cell.
· Most multiple myeloma therapies are inhibitors of the UPS (Ubiquitin Proteasome System).
· Plitidepsin's novel mechanism of action targets eEF1A2 involved in eliminating misfolded proteins in two ways (proteasome and aggresome).

Losada A et al. Plitidepsin inhibits autophagy, the main mechanism of acquired resistance to bortezomib. AACR-NCI-EORTC meeting 2017. Abstract B057.
Hotokezaka Y et al. Interaction of the Eukaryotic Elongation Factor 1A with Newly Synthesized Polypeptides. J Biol Chem 2002.
Anatoli B et al. Association of translation factor eEF1A with defective ribosomal products generates a signal for aggresome formation. J Cell Sci 2012.

IMPORTANT - See also: 3065 Plitidepsin Regulates Viability and Function of Myeloma Cells and Bone Cells in Combination with Other Anti-MM Drugs
Sunday, December 10, 2017, 6:00 PM-8:00 PM. Bldg A, Lvl 1, Hall A2 (Georgia World Congress Center)

OBJECTIVES 3

Primary:
Progression free survival according to IMWG.

Secondary:
Overall survival, response rate and duration of response.
Efficacy after crossover.
Safety profile.
Pharmacokinetic and pharmacodynamics analysis.

PATIENT CHARACTERISTICS 4

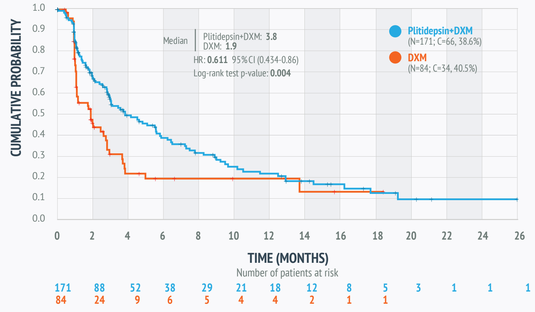
		ARM A (n=171) Plitidepsin + DXM		ARM B (n=84) DXM	
		N	%	N	%
AGE	Median (range)	64 (36-85)		65 (42-85)	
ISS stage	III	55 (33.7%)		23 (29.9)	
NUMBER OF PRIOR LINES	Median (range)	**4 (2-6)**		**4 (3-7)**	
TIME FROM DIAGNOSIS (months)		71.8 (0.1-277.2)		70.0 (19.5-178.9)	
REFRACTORY TO LAST PRIOR THERAPY		126	**73.7**	62	**73.8**
REFRACTORY	to bortezomib	98	58.7	49	58.3
	to lenalidomide	123	73.7	67	81.7
	to bortezomib and lenalidomide	**75**	**43.9**	**40**	**47.6**
	to thalidomide	66	58.4	27	50.9
	to pomalidomide	13	7.6	13	15.5
PRIOR SCT	≥1	115	67.3	55	65.5
CYTOGENETIC RISK*	High risk	45	48.9	19	44.2
	Standard risk	47	51.1	24	55.8

* Missing information in 79 patients from arm A and 41 from arm B.

Abbreviations: ISS: international staging system, SCT: stem cell transplant

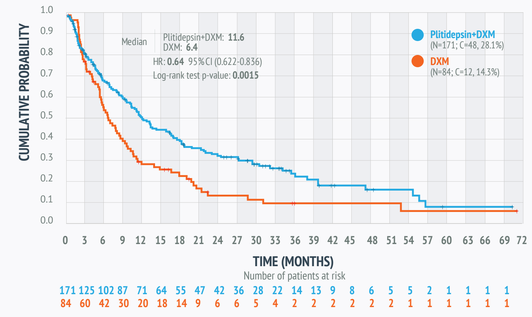
RESULTS 5

PFS WITH CONFIRMATION OF PD ACCORDING TO IA*



*IA: Investigator Assessment

OVERALL SURVIVAL. TWO STAGE METHOD. EXTENDED ANALYSIS



SAFETY 6

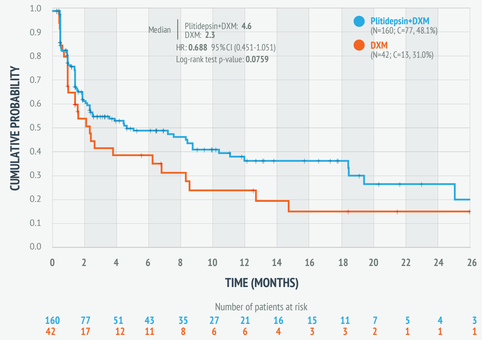
OVERALL SAFETY

GRADE 3-4 ADVERSE EVENTS AND LABORATORY ABNORMALITIES (≥5%)

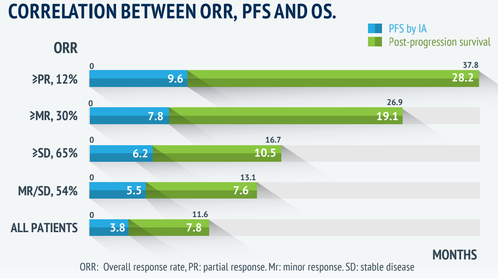
	Plitidepsin DXM %	Poma DXM (SanMiguel) %	Pano Borte DXM (Richardson) %	Daratumumab (Lonial) %	Bortezomib (Richardson) %	Lena DXM (Dimopoulos) %
Anemia	**31***	33	15	17	10	9
Thrombocytopenia	**22***	22	64	14	30	11
Neutropenia	**16***	48	14	12	14	30
Muscular weakness		5				7
Thromboembolism						11
Febrile neutropenia		10				3
Infection		34	15	6		10
Neuropathy					8	
Diarrhoea			20		7	
Myalgia	5					
CPK increased	**20***					
ALT increased	**14***					
Treatment related Discontinuation	9	4	18.2	4.7	38.4	8.8
Treatment related Deaths	**0.6**	**4.6**	**7.8**	**0**	**1.3**	**2.8**

* Laboratory abnormalities regardless of relationship

TIME TO PS DETERIORATION



CORRELATION BETWEEN ORR, PFS AND OS.



ORR: Overall response rate, PR: partial response. Mr: minor response. SD: stable disease

CONCLUSION 7

The PFS shows a statistically significant 39% risk reduction in terms of progression or death in favor of the experimental arm.

There is a statistically significant difference in OS analysis in favor of the experimental arm over the control arm once crossover effect is discounted (two-stage and RPSFT methods).

Survival results for patients with partial response (median of 37.8 months), or clinical benefit (median of 27 months), as well as the survival of 17 months in patients with disease control rate (found in 65% of patients) are of relevance in the setting of an extensively pretreated MM patient population, where the expected median survival is about nine months.

Plitidepsin with dexamethasone is well-tolerated and most of adverse events were manageable. This new treatment regimen of **plitidepsin** + DXM introduces a valuable therapeutic option with a novel mechanism of action, expanding the therapeutic armamentarium of multiple myeloma as most of patients who become resistant to proteasome inhibition tend to overexpress eEF1A2, the target of **plitidepsin.**

DISCLOSURES

Dr. Spicka: Celgene: Research Funding; Celgene, Amgen, BMS, Janssen, Takeda, Sanofi: Honoraria; Celgene, Amgen, BMS, Janssen, Takeda, Sanofi, Pharmamar: Speakers Bureau. **Dr. Ocio**: Novartis: Consultancy, Honoraria; Takeda: Consultancy, Honoraria; AbbVie: Consultancy; Pharmamar: Consultancy; Seattle Genetics: Consultancy; Array Pharmaceuticals: Research Funding; Mundipharma: Research Funding; Celgene: Honoraria, Research Funding; Amgen: Honoraria, Research Funding; Sanofi: Research Funding; BMS: Honoraria; Janssen: Honoraria. **Dr. Oakervee:** There are no relationships to disclose. **Dr. Greil:** Roche: Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support, Research Funding; Novartis, Celgene: Research Funding; Takeda: Honoraria, Research Funding; BMS, Amgen: Honoraria. **Dr. Banh:** PharmaMar, Bristol Myers Squibb: Membership on an entity's Board of Directors or advisory committees; Bristol Myers Squibb, Specialised Therapeutics, ApoPharma, Novartis: Honoraria; Celgene, AstraZeneca, Pharmacyclics: Research Funding. **Dr. Catley:** There are no relationships to disclose. **Dr. Huang:** Celgene International Sàrl: Research Funding. **Dr. D'Rozario:** Roche: Consultancy. **Dr. Dimopoulos:** Amgen Inc, Celgene Corporation, Janssen Biotech Inc, Onyx Pharmaceuticals, an Amgen subsidiary, Takeda Oncology: Consultancy, Honoraria, Other: Advisory Committee: Amgen Inc, Celgene Corporation, Janssen Biotech Inc, Onyx Pharmaceuticals, an Amgen subsidiary, Takeda Oncology; Novartis: Consultancy, Honoraria; Genesis Pharma: Research Funding. **Dr. Rodríguez:** PharmaMar: Employment. **Dr. Martinez:** PharmaMar: Employment. **Extremera:** PharmaMar: Employment. **Alfaro:** PharmaMar: Employment. **Dr. Carella:** There are no relationships to disclose. **Dr. Meuleman**: Amgen, Celgene, Janssen: Membership on an entity's Board of Directors or advisory committees. **Dr. Hájek**: Amgen, Takeda, BMS, Celgene, Novartis, Janssen: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; Abbvie: Consultancy, Honoraria; PharmaMar: Consultancy, Honoraria. **Dr. Symeonidis**: There are no relationships to disclose. **Dr. Min**: There are no relationships to disclose. **Dr. Cannel**: There are no relationships to disclose. **Dr. Ludwig**: Takeda: Consultancy, Research. **Dr. Sonneveld**: There are no relationships to disclose. **Dr. Mateos**: There are no relationships to disclose.