National Securities Market Comission
Markets Directorate General
c/ Edison núm. 4
28006 Madrid

Colmenar Viejo (Madrid), December 11, 2017

Pursuant to article 228 of the consolidated text of the Spanish Securities Market Act, we hereby inform you of the following **SIGNIFICANT EVENT**:

"Pharma Mar has presented positive results from the ADMYRE Phase III pivotal trial of plitidepsin in combination with dexamethasone versus dexamethasone alone in patients with relapsed or relapsed and refractory multiple myeloma at the 59th American Society of Hematology annual Meeting & Exposition from December 9th to 12th in Atlanta. In the Significant Fact nº 236798 dated March 31st of 2016, PharmaMar already announced the trial met its primary endpoint (progression free survival).

In this regards please find attached press release that Pharma Mar, S.A. will distribute to the media today together with the two attached slides".

PharmaMar presents positive results of the pivotal Phase III trial with plitidepsin in multiple myeloma during the ASH meeting

- As previously informed, the Phase III trial, ADMYRE, which compared plitidepsin in combination with dexamethasone versus dexamethasone alone met its primary endpoint, progression free survival, and secondary objectives, overall survival and safety

- With regards to the primary endpoint, in patients who received the combination of plitidepsin with dexamethasone, a 3.8 month progression free survival (PFS) was observed in comparison to 1.9 months with dexamethasone alone, according to the investigator´s assessment

- With respect to overall survival, all patients obtained an overall survival that almost doubled the comparative with dexamethasone (11.6 months versus 6.4 months). In patients that experimented stable disease (65%), overall survival was 17 months

- With reference to safety, PharmaMar presented a comparative table on adverse events in which plitidepsin was shown to be better tolerated than other drugs already used for multiple myeloma

- Quality of Life evolution, this being evaluated according to a deterioration in the performance status, was better in patients treated with the combination of plitidepsin plus dexamethasone

- A novel mechanism of action was also presented, demonstrating that plitidepsin is complimentary to actual treatments

- Plitidepsin reduces the number of osteoclasts and inhibits its function. Osteoclasts are the cells responsible for bone destruction in multiple myeloma. This data, from a preclinical study, were also presented during ASH ((poster #3065)

Madrid, 11th December, 2017. PharmaMar (MSE: PHM) has presented positive results from the ADMYRE Phase III pivotal trial of plitidepsin in combination with dexamethasone versus dexamethasone alone in patients with relapsed or relapsed and refractory multiple myeloma. The data presented at the 59th American Society of Hematology annual Meeting & Exposition from December 9th to 12th in Atlanta, was already submitted to the EMA in the framework of the assessment process of the Marketing Authorization Application (MAA) for plitidepsin.

The poster entitled *"Randomized Phase III Study (ADMYRE) of plitidepsin in combination with dexamethasone vs. dexamethasone alone in patients with relapsed/refractory multiple myeloma"* presents the data obtained from the ADMYRE pivotal study that enrolled 255 patients, after at least three, but no more than six prior therapeutic regimens, from 83 medical centers across 19 countries (including the U.S, Europe and Asia-Pacific). On March 31st of 2016[i], PharmaMar announced the study met its primary endpoint.

In the group of patients who received the combination of plitidepsin with dexamethasone (n=171), according to the investigator´s assessment, a 3.8 month progression free survival (PFS) was observed in comparison to 1.9 months on dexamethasone alone. According to the Independent Review Committee (IRC), the progression free survival was 2.6 months for the combination versus 1.7 months for the dexamethasone monotherapy arm. The study met its primary endpoint, this being the improvement of progression free survival. Plitidepsin showed a statistically significant reduction in the risk of progression over the comparator.

With regards to overall survival (OS), a statistically significantly superior increase in the plitidepsin plus dexamethasone arm was observed according to the two-stage *Latimer et al* method. In the patients that received the combination with plitidepsin, the registered overall survival was 11.6 months against the 6.4 months of the comparator. According to the IRC, the objective response rate (partials + best response) in the patients that received plitidepsin was 13.8%, with a median duration of response of 12 months. In the patients that responded to the treatment of plitidepsin with dexamethasone (12%), the registered median overall survival was of 37.8 months, and in those that reached stable disease (65%) the OS was 17 months.

Safety data

With regards to adverse effects, the hematological toxicity was low. The most common toxicities, hepatic and muscular, were transient and in a majority of cases were reversible and manageable when applying a dose adjustment.

One of the most common grade 3-4 treatment-related adverse events (% of patients in Arm A/Arm B) was myalgia (5%/0%). The most common grade 3-4 hematological/non-hematological adverse events (% of patients in Arm A/Arm B) were: anemia (31%/35.4%), thrombocytopenia (22%/27.9%), neutropenia (16%/5.1%), CPK increase (20%/0%), ALT increase (14%/0%) and AST increase (9%/0%). Most of these events were transient and reversible. 15 patients (9%) discontinued treatment due to treatment-related adverse events in Arm A; 3 (6.5%) in Arm B.

During the presentation of the results at the ASH meeting, a comparative on the treatment related deaths of different compounds already approved for multiple myeloma: plitidepsin with dexamethasone, 0.6%; pomalidomide with dexamethasone, 4.6%[ii]; panobinostat with bortezomib and dexamethasone, 7.8%[iii]; daratumumab, 0%[iv]; bortezomib, 1.3%[v]; and lenalidomide with dexamethasone, 2.8%[vi].

In the ADMYRE study, the evolution of performance status was evaluated, this meaning that the time that patients took for their physical condition to deteriorate and that this affected their everyday life from the beginning of the study was calculated. The patients treated in the plitidepsin plus dexamethasone arm took double the time to performance status (PS) (4.6 months) in comparison to dexamethasone as a single agent (2.3 months).

Mechanism of action of plitidepsin

The target of plitidepsin is the eEF1A2 protein. The bonding of plitidepsin to this protein blocks its pro-oncogenic property and impedes the transportation of the misfolded proteins, which are toxic to the tumor, to the proteasome for their destruction. It also inhibits the activation of the aggresome by eEF1A2 and the destruction of the aggresome in the lysosome. This provokes an excess of misfolded proteins, this causing cell death through apoptosis. Other treatments are complementary to plitidepsin and they are going to block the proteasome or the cereblon that identifies the misfolded proteins.

In another *in vitro* study that PharmaMar has also presented at the ASH Congress,

it is concluded that plitidepsin also has the capability of cancelling out the activity of the osteoclasts, the cells responsible for bone destruction, in a concentration of up to 100 times less to that which is considered necessary for the elimination of myeloma cells.

About plitidepsin

Plitidepsin is currently in clinical development for hematological cancers, including a Phase Ib trial in relapsed or refractory multiple myeloma as a triple combination of plitidepsin and bortezomib, and a Phase II in patients with multiple myeloma refractory to lenalidomida and bortezomib. Furthermore, a Phase II study in relapsed or refractory angioimmunoblastic T-cell lymphoma. A Phase III trial in multiple myeloma relapsed or refractory has been completed. Plitidepsin has received orphan drug designation in the European Union and the United States of America.

About multiple myeloma

Multiple myeloma is a relatively uncommon type of blood cancer, which accounts for 10% of all hematological malignancies, this being caused by malignant plasma cells that very rapidly multiply[vii]. Normal plasma cells are white blood cells, which form part of the immune system, found in the bone marrow that produce the antibodies necessary for fighting infections[viii]. Abnormal cells produce a type of antibody that does not benefit the body and accumulate, thus preventing normal cells from functioning properly. In 2015, 26,850 new cases were diagnosed in the US, and about 11,200 people died from this disease[ix].In Europe, the incidence is 4.5–6.0 out of 100 000 diagnosed per year[x].

About PharmaMar

Headquartered in Madrid, PharmaMar is a world-leading biopharmaceutical company in the discovery and development of innovative marine-derived anticancer drugs. The company has a pipeline of drug candidates and a robust R&D oncology program. PharmaMar develops and commercializes YONDELIS® in Europe and has other clinical-stage programs under development for several types of solid and hematological cancers, Zepsyre™ (PM1183), plitidepsin, PM184 and PM14. PharmaMar is a global biopharmaceutical company with subsidiaries in Germany, Italy, France, Switzerland, United Kingdom, Belgium, Austria and the United States. PharmaMar fully owns other companies: GENOMICA, leading molecular diagnostics company; Sylentis, dedicated to researching therapeutic applications of gene silencing (RNAi); and two other chemical enterprises, Zelnova Zeltia and Xylazel. To learn more about PharmaMar, please visit us at www.pharmamar.com.

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[i] http://www.pharmamar.com/wp-content/uploads/2016/03/PR_Positive-Results_ADMYRE.pdf

[ii] San Miguel J, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol (2013) 14 (11): 1055-66.

[iii] Richardson PG, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood (2013) 122 (14): 2331-7. Richardson PG, et al. Panobinostat plus bortezomib and dexamethasone in previously treated multiple myeloma: outcomes by prior treatment. Blood (2016) 127 (6): 713-21.

[iv] Lonial S, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet (2016) 387 (10027): 1551-60.

[v] Richardson PG, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med (2005) 352 (24): 2487-98.

[vi] Dimopoulos M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med (2007) 357 (21): 2123-32.

[vii] http://www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-what-is-it

[viii] http://www.myeloma.org.uk/information/what-is-myeloma/

[ix] http://seer.cancer.gov/statfacts/html/mulmy.html

[x] http://www.esmo.org/Guidelines/Haematological-Malignancies/Multiple-Myeloma

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.

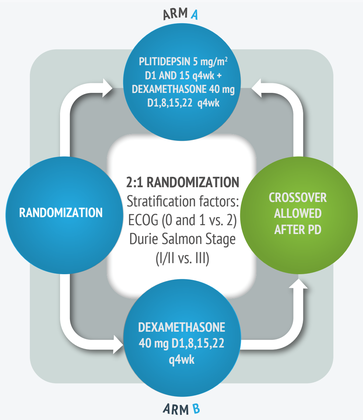
STUDY DESIGN 2

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

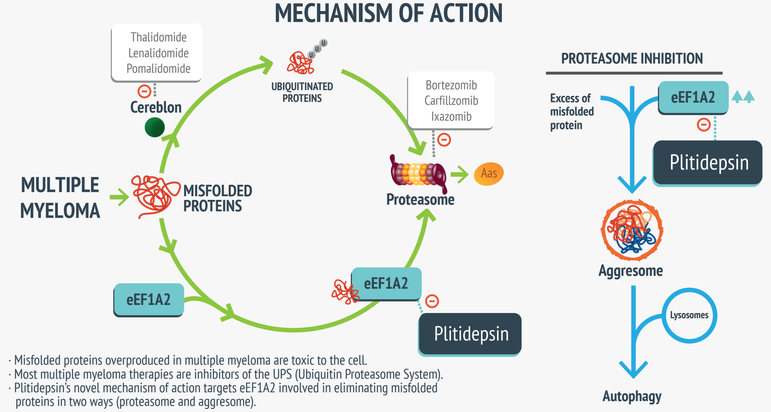


Hematological parameters:
ANC ≥ 1.0 x 10^9/l
Platelet count ≥ 50 x 10^9/l
Hemoglobin ≥ 8.5 g/dL

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

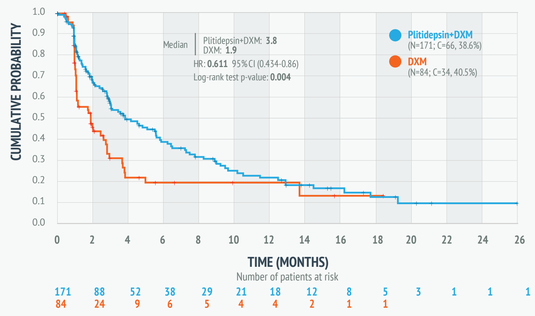
		ARM A (n=171) Plitidepsin + DXM		ARM B (n=84) DXM	
		N	%	N	%
AGE	Median (range)	64 (36-85)		65 (42-85)	
ISS stage	III	55 (33.7%)		23 (29.9)	
NUMBER OF PRIOR LINES	Median (range)	**4 (2-6)**		**4 (3-7)**	
TIME FROM DIAGNOSIS (months)		71.8 (0.1-277.2)		70.0 (19.5-178.9)	
REFRACTORY TO LAST PRIOR THERAPY		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

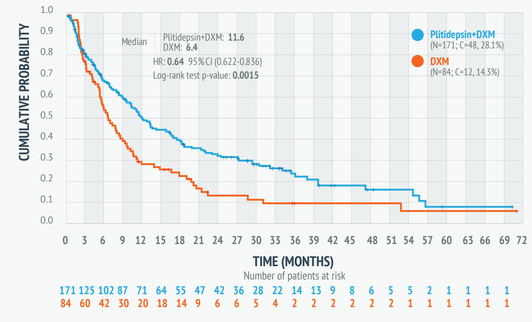
RESULTS 5

PFS WITH CONFIRMATION OF PD ACCORDING TO IA*



*IA: Investigator Assessment

OVERALL SURVIVAL. TWO STAGE METHOD. EXTENDED ANALYSIS



SAFETY 6

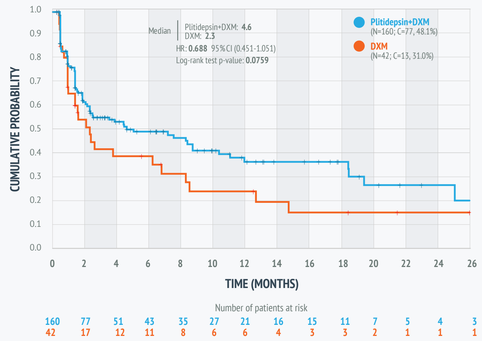
OVERALL SAFETY

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

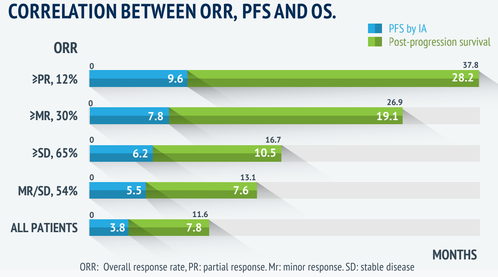
	Plitidepsin DXM %	Poma DXM (SanMiguel) %	Pano Borte DXM (Richardson) %	Daratumumab (Lonial) %	Bortezomib (Richardson) %	Lena DXM (Dimopoulos) %
Anemia	**31***	33	15	17	10	9
Thrombocytopenia	**22***	22	64	14	30	11
Neutropenia	**16***	48	14	12	14	30
Muscular weakness		5				7
Thromboembolism						11
Febrile 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).

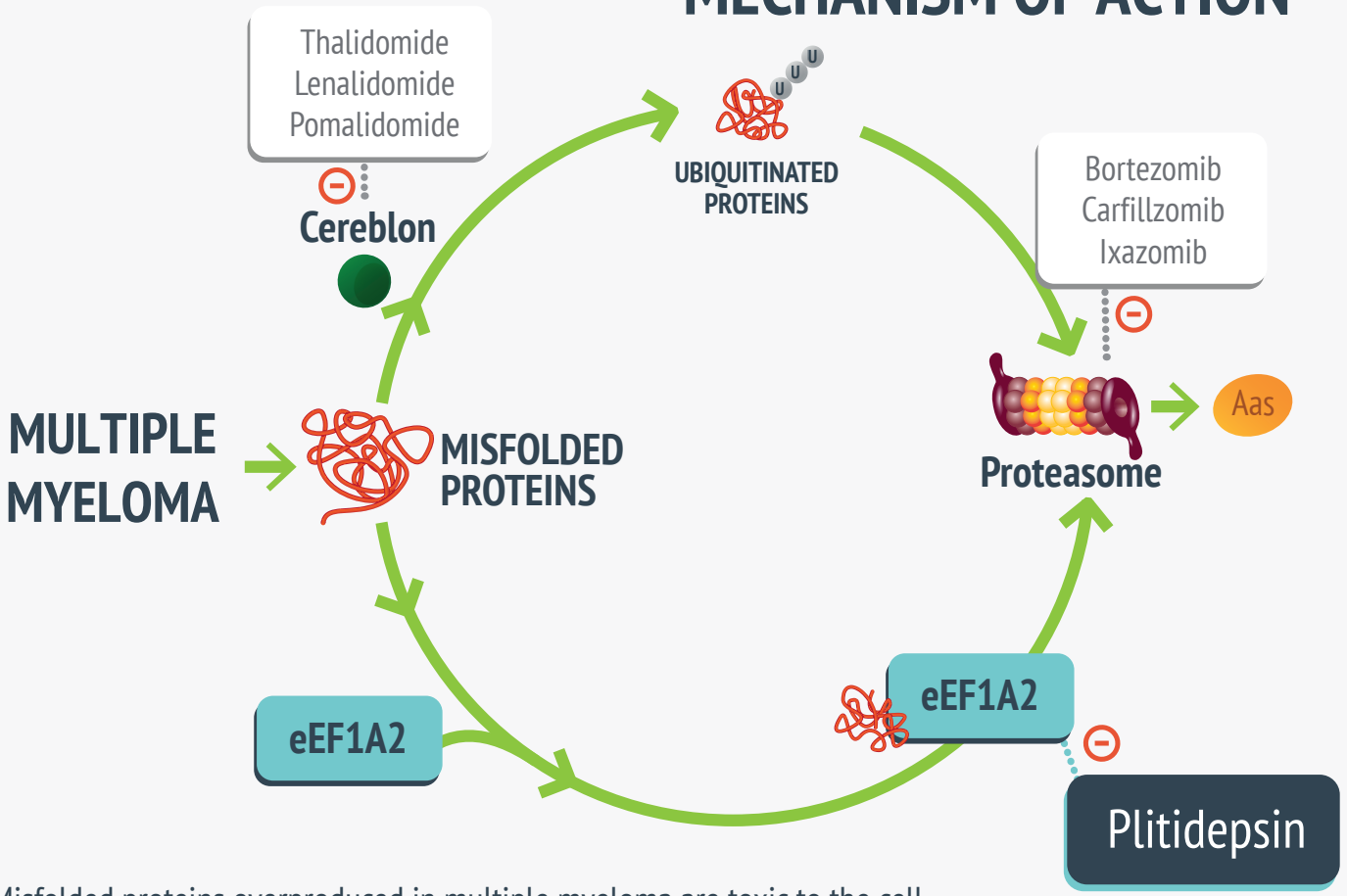
Survival results for patients with partial response (median of 37.8 months), or clinical benefit (median of 27 months), as well as the survival of 17 months in patients with disease control rate (found in 65% of patients) are of relevance in the setting of an extensively pretreated MM patient population,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

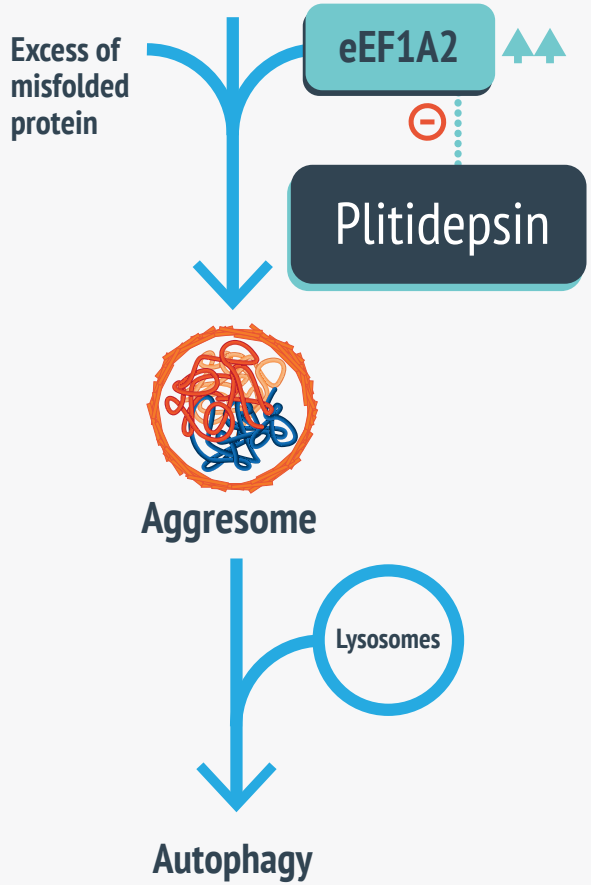
DISCLOSURES

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.

MECHANISM OF ACTION



PROTEASOME INHIBITION



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