Proteasome inhibitors: Really a targeted therapy?

Dolors Colomer, Patricia Pérez-Galán, Gaël Roué.

Unitat d' hematopatologia, Hospital Clinic, Institut d' Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.

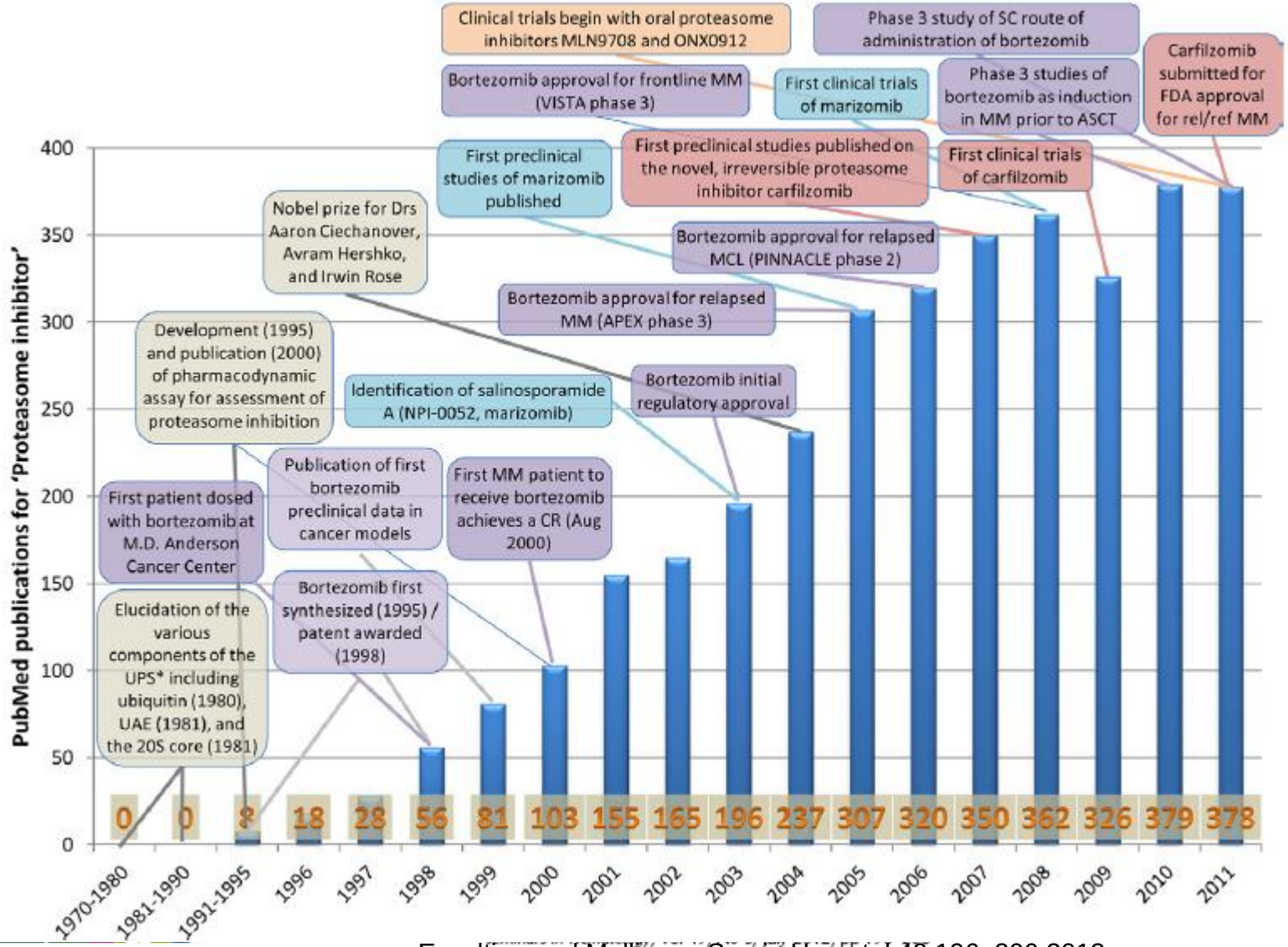
Disclosure slide

- I have no Conflicts of Interest to declare

- **Proteasome inhibitors** were not initially considered as drug candidates at all, due to the assumption that the inhibition of this basic cellular pathway would disrupt the homeostasis of all tissues.

- This view was overturned by the discovery that proteasome inhibition preferentially induced apoptosis in transformed cells, ie, rapidly proliferative cells with deregulated cell cycle or other signaling, or cells with abnormally upregulated activities.

Timeline of the evolution of proteasome inhibition



Esseltine and Mulligan, Semin Hematol 49:196–206,2012

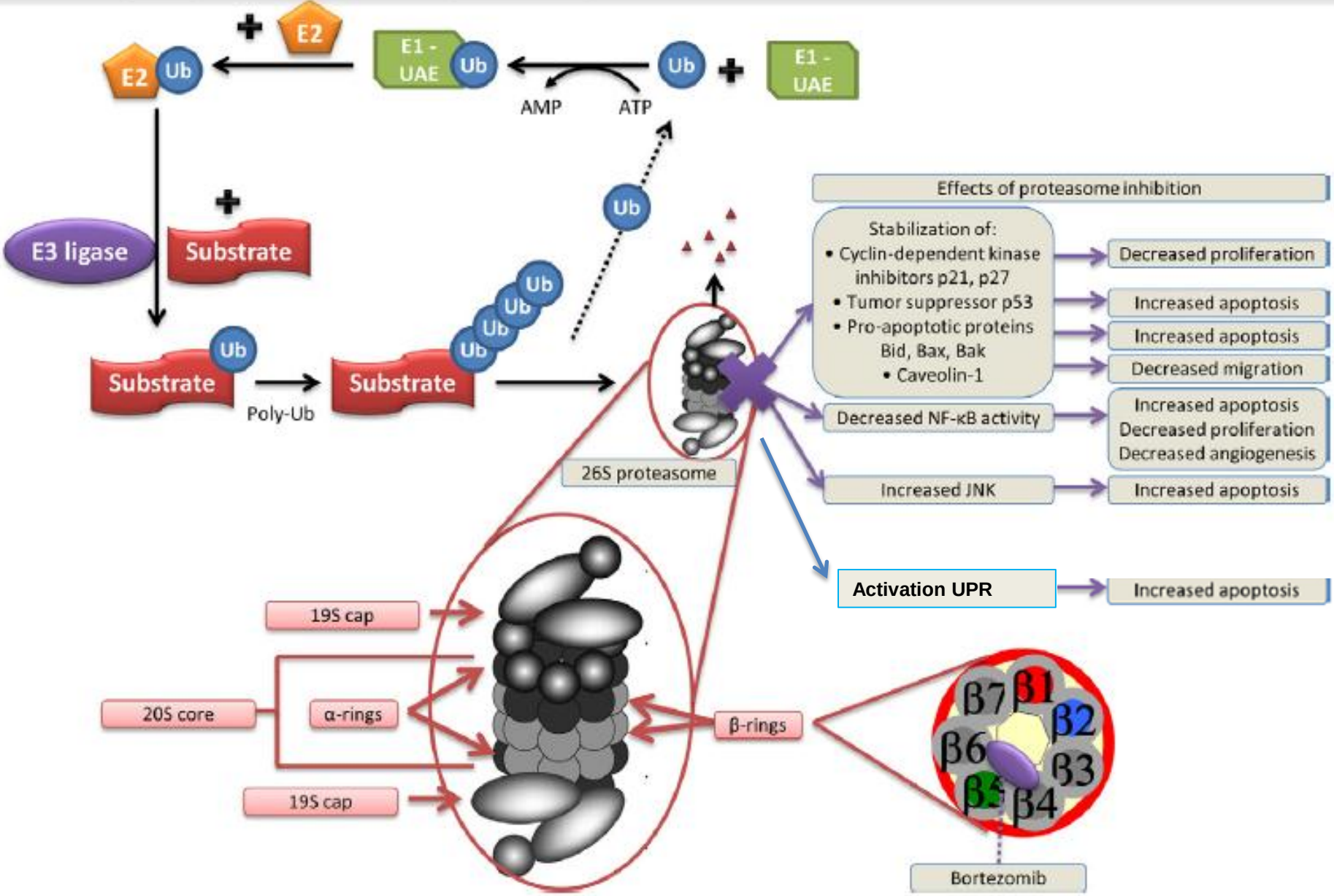


Figure 2. The ubiquitination pathway in the UPS results in the polyubiquitination of substrate proteins, which are recognized and unfolded by the 19S cap and then degraded into peptide fragments within the 20S core; bortezomib inhibits proteolysis at the β5-site, resulting in multiple downstream effects.

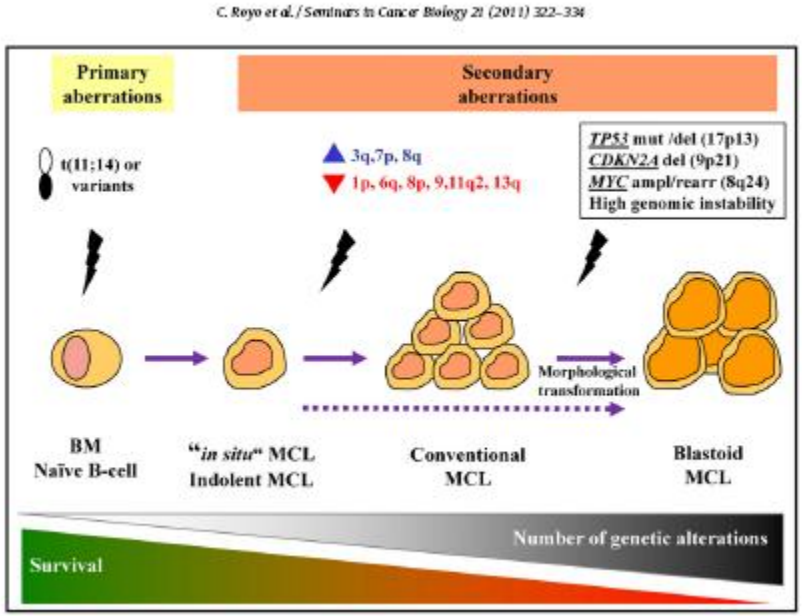
Modified from Semin Hematol 49:196–206,2012

- **Bortezomib** has demonstrated substantial benefit alone or as part of combinations inducing chemo- or radiosensitization in several hematological malignancies, mainly in multiple myeloma and mantle cell lymphoma

- Less effective in solid tumors

Mantle Cell Lymphoma (MCL): disease features and biology

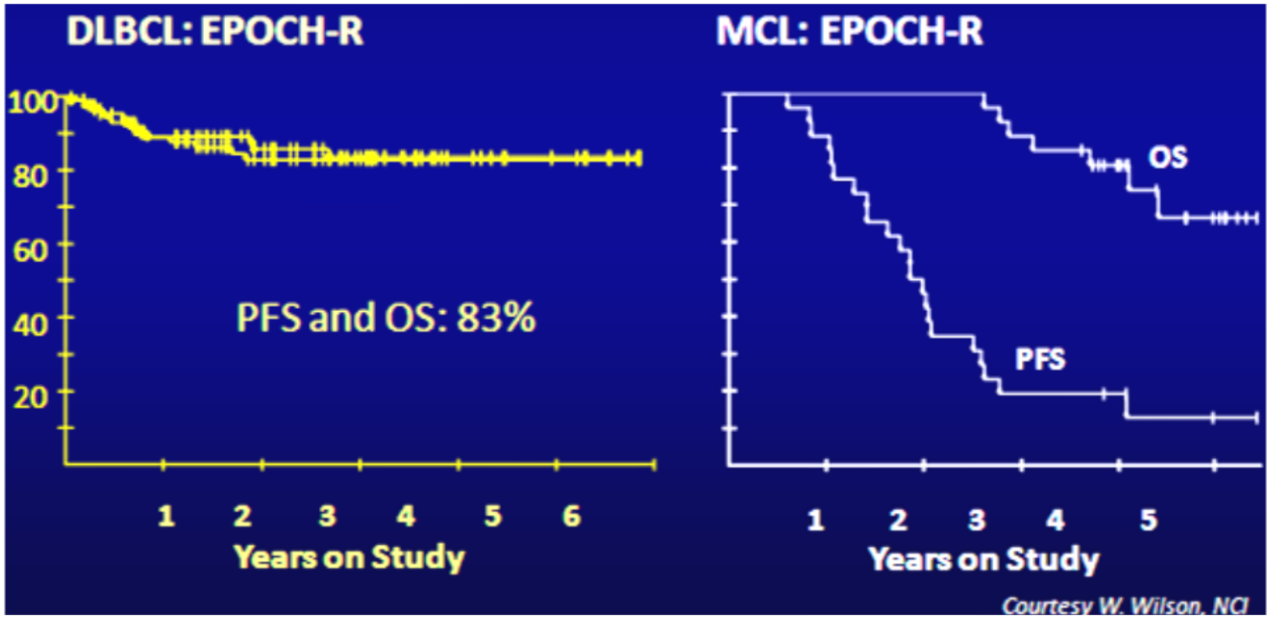
- ✓ Mature B-cell phenotype (CD19, CD20, CD22, CD79) and coexpression of CD5.
- ✓ Genetic hallmark t(11;14)(q13;q32) **Cyclin D1** overexpression
- ✓ Many secondary genomic aberrations :
  - Cell cycle and senescence: BMI-1/INK4/ARF/CDK4/RB
  - DNA damage: ATM/CHK2/p53



- ✓ Up to 30% of MCL show leukemic involvement

Mantle Cell Lymphoma: current therapies

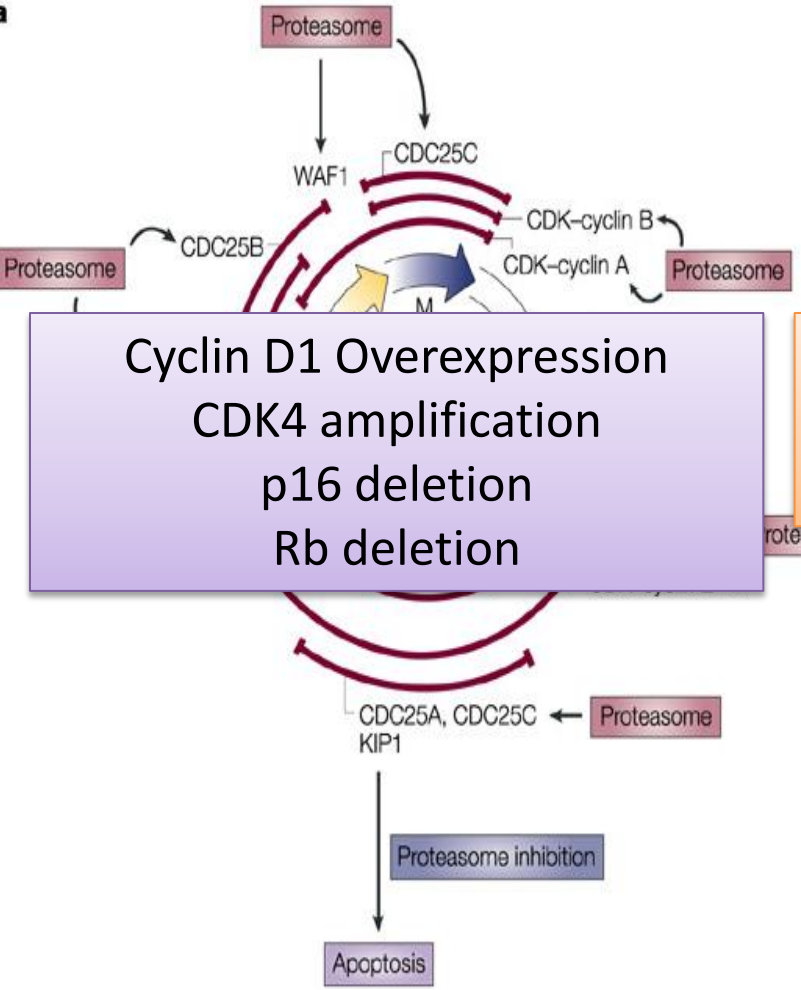
- Intensive immuno-chemotherapy regimens, highly effective in other aggressive lymphomas such as DLBCL , induces only transient remissions in MCL



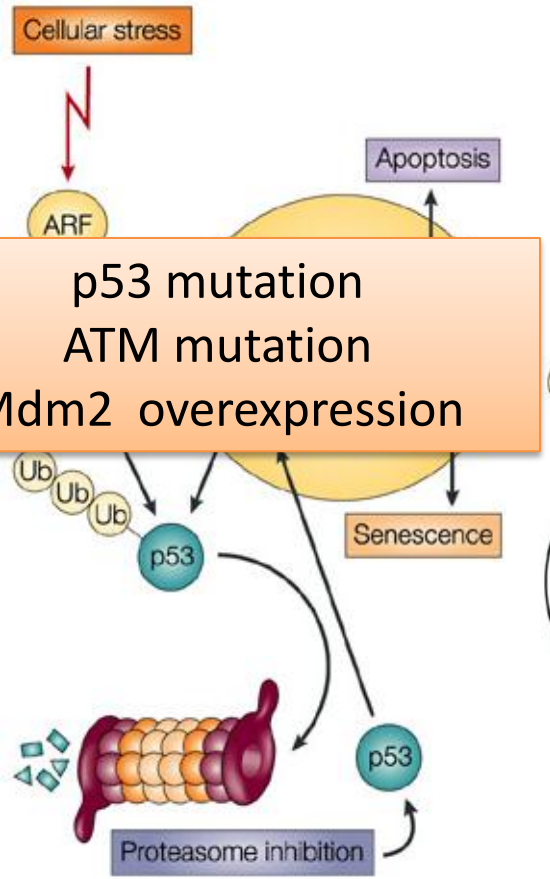
EPOCH-R: Etoposide, doxorubicin, Vincristine, prednisone cyclophosphamide and rituximab

Bortezomib: initial rationale to use in MCL

Cell cycle (CDK-cyclin complexes) **p53** **NF-κB**



Cyclin D1 Overexpression
CDK4 amplification
p16 deletion
Rb deletion



p53 mutation
ATM mutation
Mdm2 overexpression

It has shown that bortezomib does not block constitutive NF-kB activity in MCL and MM

(*Hideshima, Blood 2009; Markomina, Mol Cancer Res ; Yang, Mol Cancer 2008)*

Adams, J. *Nat Rev Cancer* 2004; 4 :349

Bortezomib induces remissions in relapsed and refractory MCL

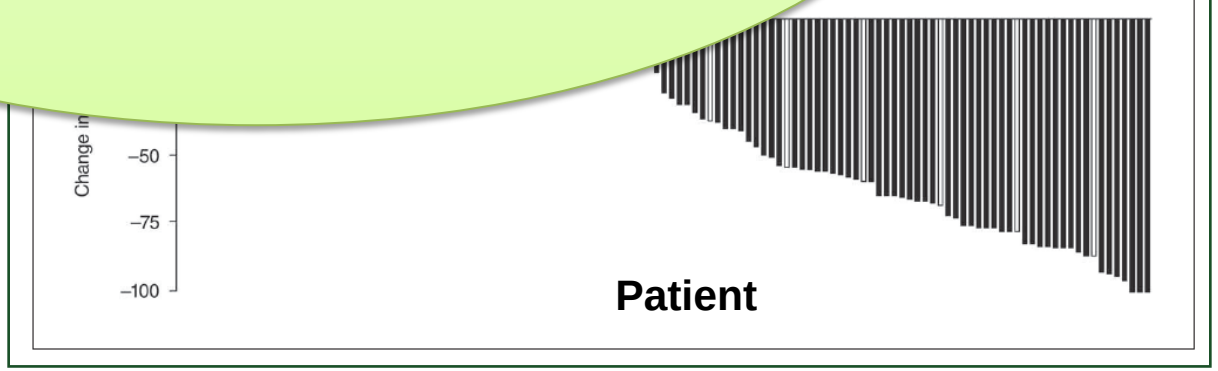
1.5 mg/m^2
Response rate 41
Time to resp

Patients *Goy A, JCO 2005*
nnor O, JCO 2005

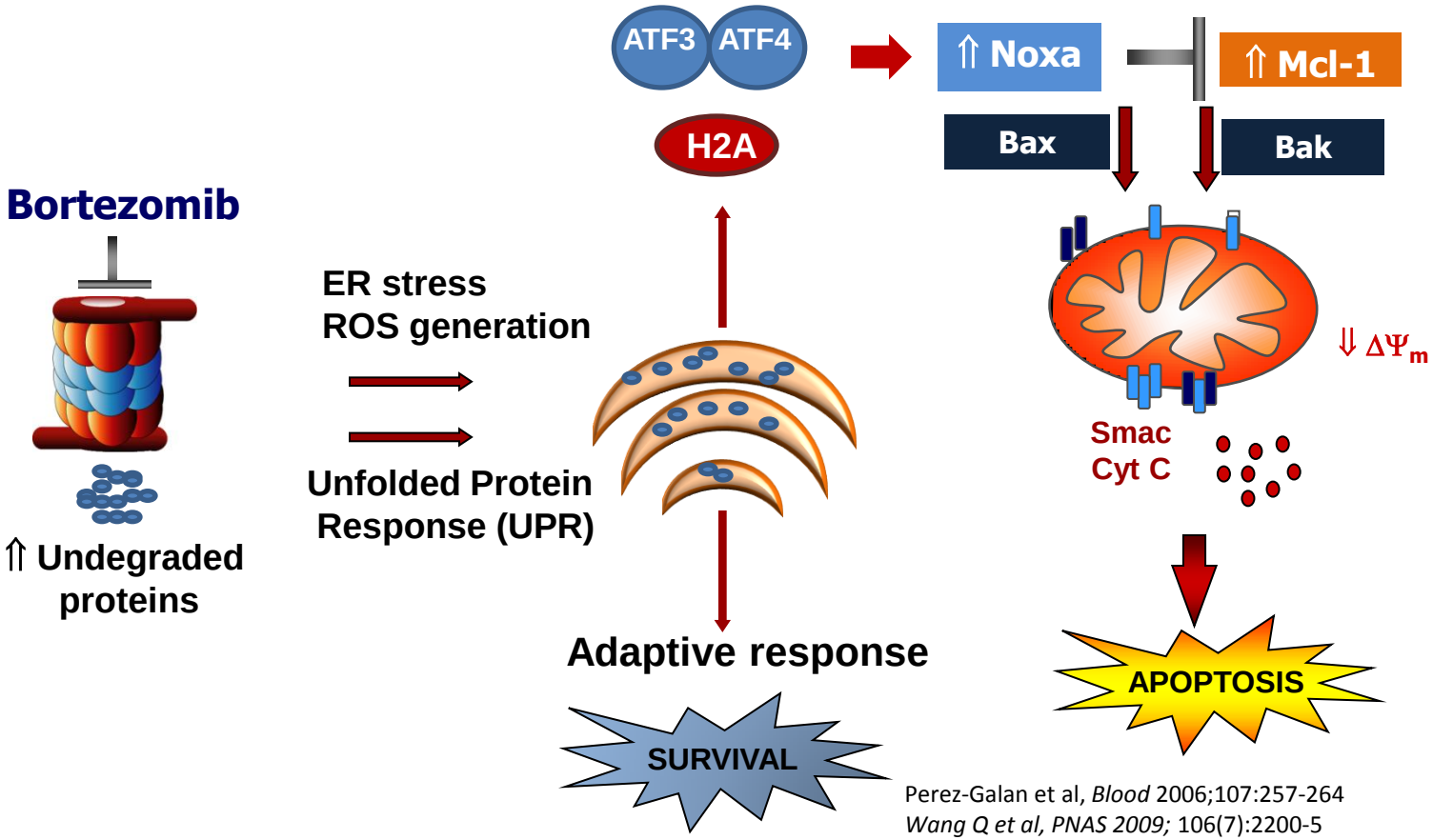
FDA approval in 2006 as second line treatment in MCL

LE study)

onths
, JCO 2006



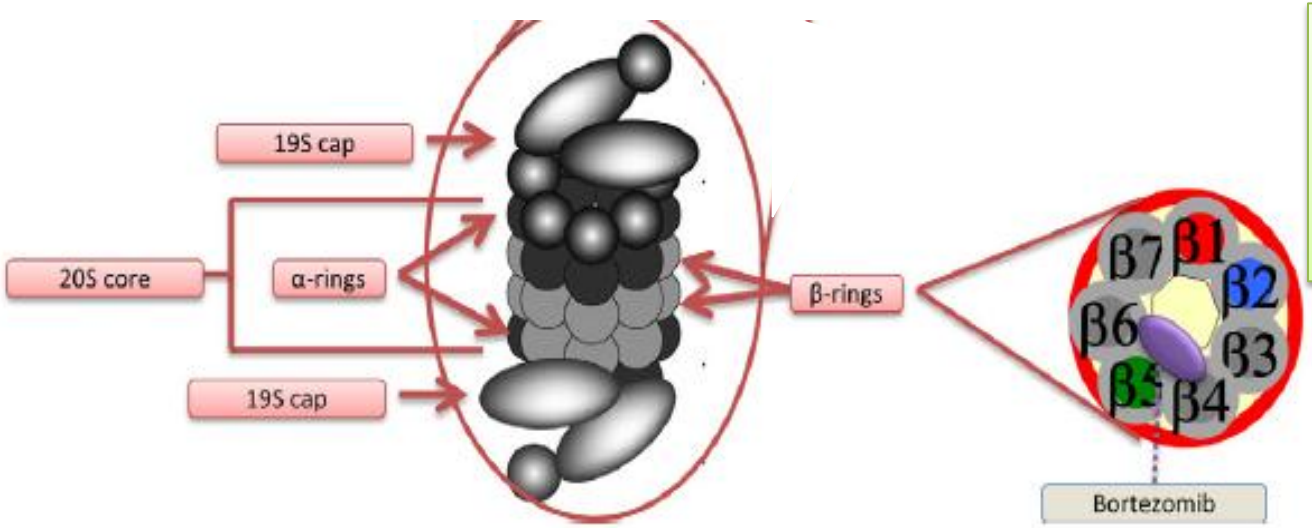
Bortezomib: proposed mechanism of action



Perez-Galan et al, *Blood* 2006;107:257-264
Wang Q et al, PNAS 2009; 106(7):2200-5
Weniger et al, *CCR* 2011. 17(15):5101-12

However, still more than half of MCL cases fail to respond to bortezomib

The explanation for these differential responses remains unanswered



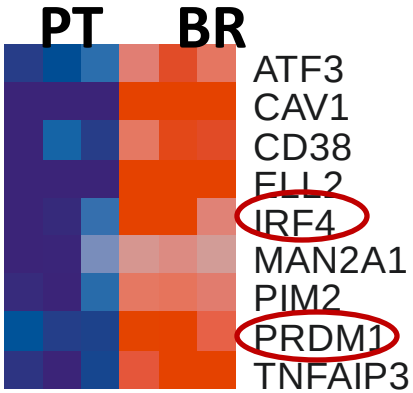
1. Point mutations or overexpression of β5 (PSMB5) subunit in MM
2. High proteasome activity

Oelermans R, Blood 2008; Ruckrich T, Leukemia 2009; Lu S, Exp Hematol 2009, Ri M, Leukemia 2010; Lü S, Exp Hematol 2011; Franke N.E, Leukemia 2011

BR cell lines have acquired a partial plasmacytic phenotype without full differentiation to plasma cells

IRF4 high plasma cell *vs* B-cell

HBL2



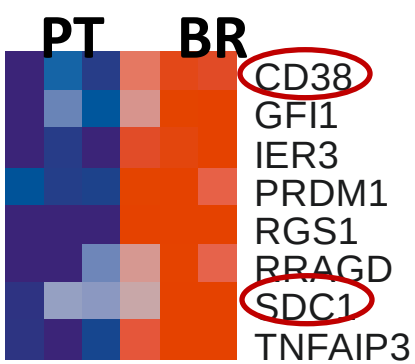
FDR=0.04; NES= 1.44

JEKO

FDR<0.001; NES= 1.91

Plasma cell *vs* B-cell

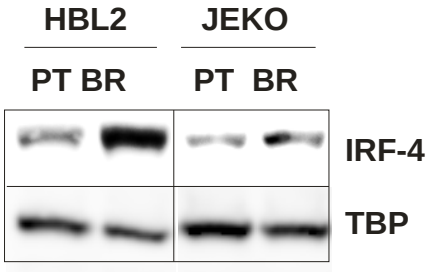
HBL2



FDR=0.08; NES =1.52

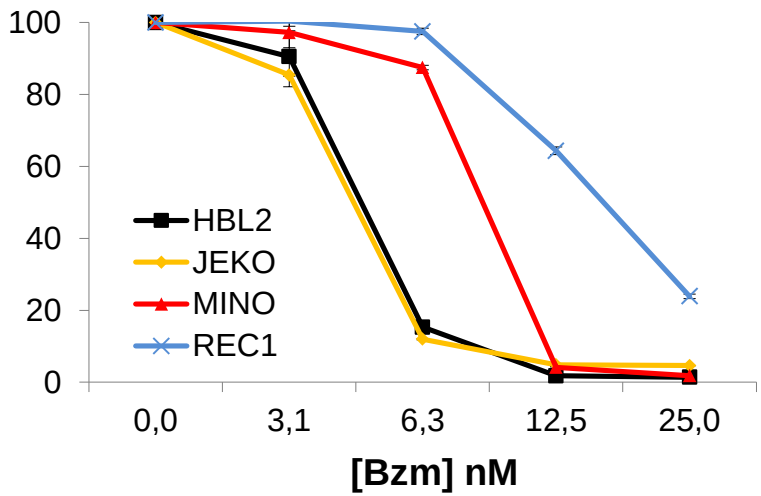
JEKO

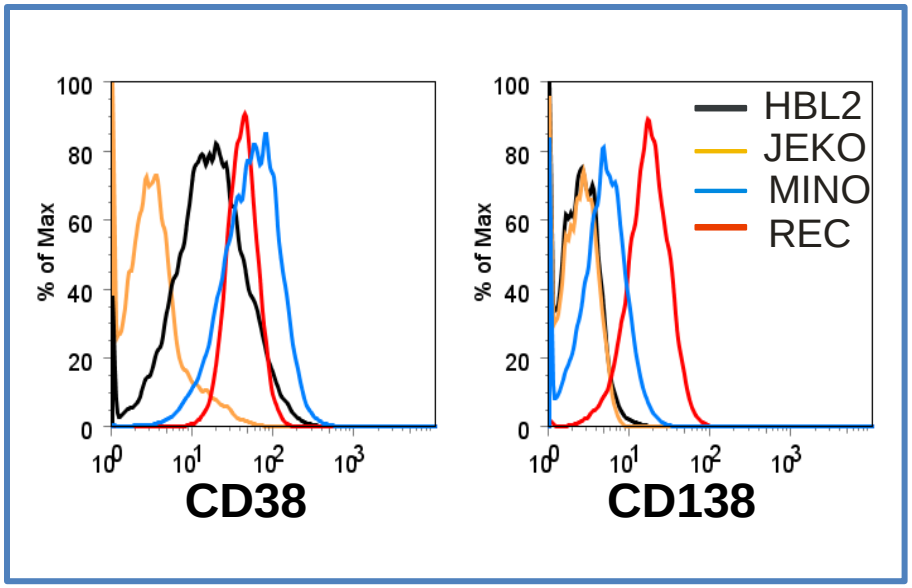
FDR=0.03; NES= 1.65



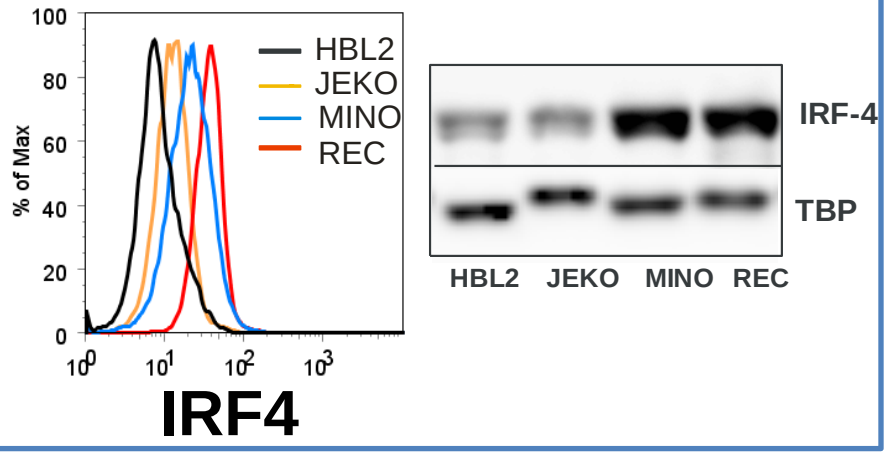
Pérez-Galán et al. Blood 2011;117(2):542-52

Intrinsic bortezomib resistance MCL cell lines (MINO and REC) show plasmacytic features





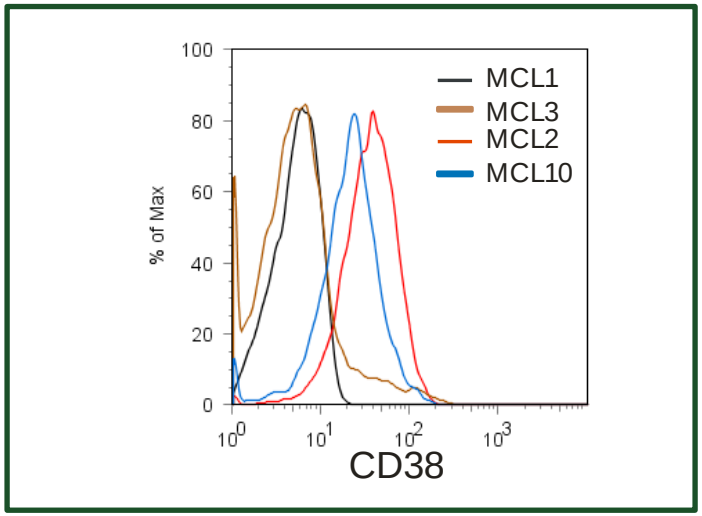
IRF4 is highly expressed in MINO and REC

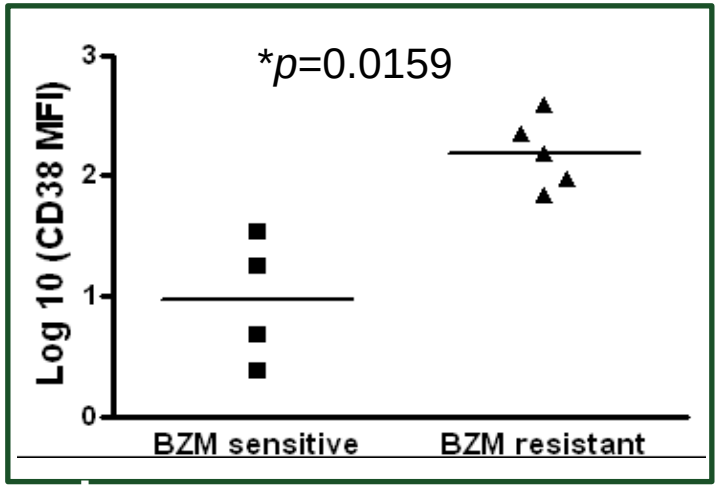


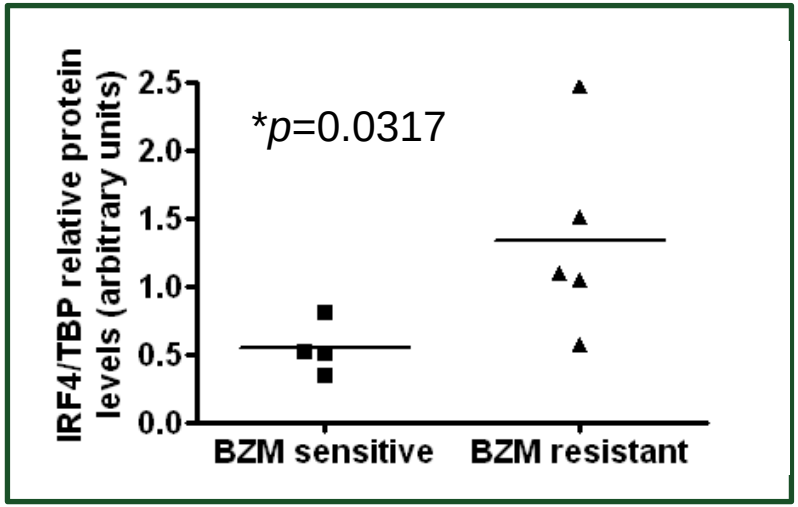
XBP-1 is not spliced in MINO and REC

Pérez-Galán et al. Blood 2011;117(2):542-52

Bortezomib resistant MCL patients show higher CD38 and IRF4 expression







VIENNA 2012 ESMO congress

www.esmo2012.org

Pérez-Galán et al. Blood 2011;117(2):542-52

Paradox

MCL with features of partial plasma cell differentiation (upregulation of IRF4 and CD38)

Bortezomib resistant

?

MM (Plasma Cells)

Bortezomib sensitive

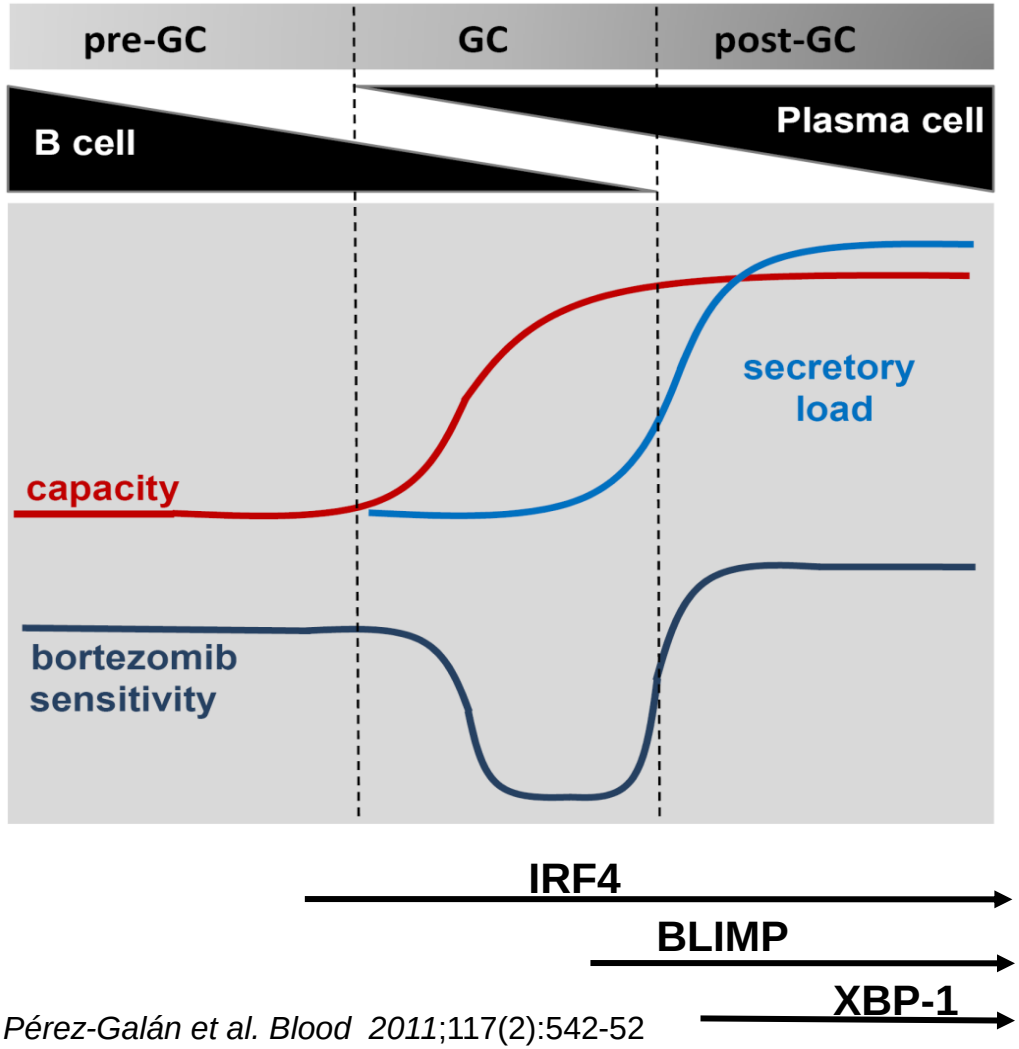
SECRETION

Cancer Res 2007; 67: (4). February 15, 2007

Extensive Immunoglobulin Production Sensitizes Myeloma Cells for Proteasome Inhibition

Silke Meister,[1] Ulrich Schubert,[3] Kirsten Neubert,[1] Kai Herrmann,[4] Renate Burger,[5] Martin Gramatzki,[5] Sabine Hahn,[3] Sandra Schreiber,[3] Sabine Wilhelm,[1] Martin Herrmann,[2] Hans-Martin Jäck,[4] and Reinhard E. Voll[1,2]

A model for bortezomib resistance in MCL



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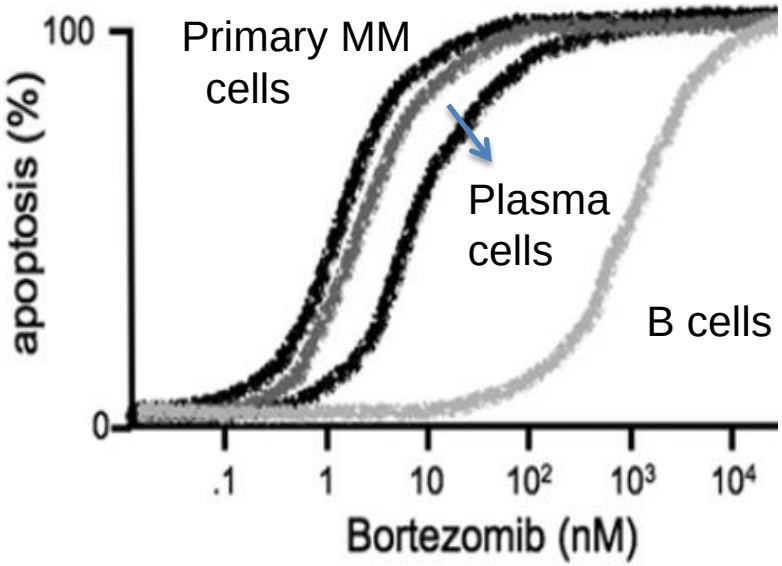


Cenci et al, Semin Hematol 49:215–222,2012

Advantages bortezomib

- Malignant cells harbor elevated proteasome activity compared with normal cells.
- Cancer cells are more dependent on proteasome activity for their survival and drug resistance; therefore, malignant cells should be more sensitive to treatment with proteasome inhibitors.
- Bortezomib sensitizes cancer cells to conventional chemotherapeutic agents, and appears to overcome drug resistance.

HSP inhibitors

Tanespimycin
Retaspimycin

Farnesyl transferase inhibitors (FTIs)

Tipifarnib
Lanafarnib

Deacetylase inhibitors (DACI)

Vorinostat
Panabinostat
Belinostat
Romidepsin

Immuno modulating agents

Thalidomide
Lenalidomide
Pomalidomide

AKT/mTOR inhibitors

Perifosine
Tensirolimus
Everolimus

DNA damaging agents

Alkylators
Antracyclines
bendamustine

Pan-BCL2 inhibitors

Obatoclax

Monoclonal antibodies

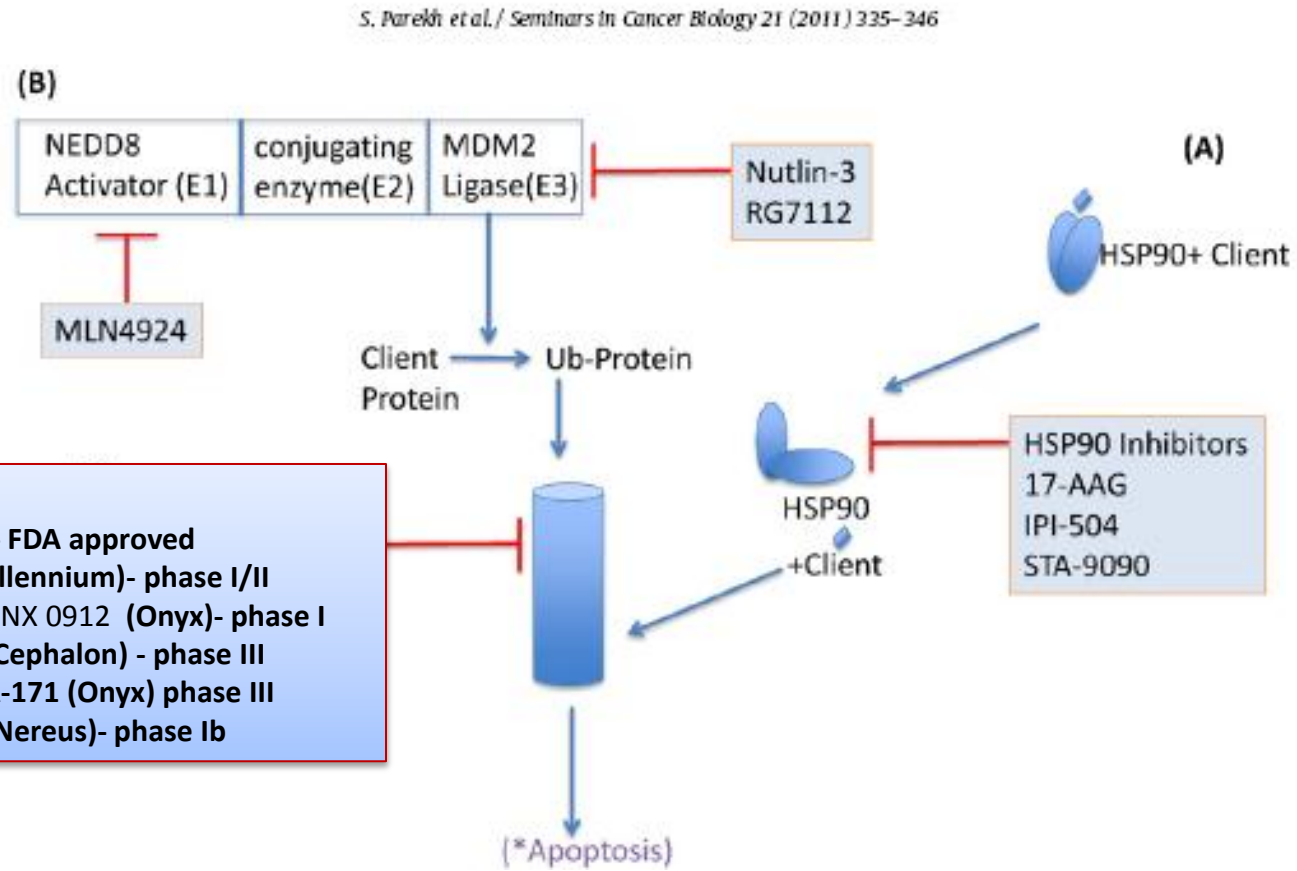
Elotuzumab (CD319)
Mapatumumab (trail receptors)
Siltuximab (IL-6)

Disadvantages bortezomib

- **Toxic side effects** (asthenia, gastrointestinal events, hematological toxicity, peripheral neuropathy and a high rate of shingles).
- Bortezomib is particularly effective in MM and MCL. However, **only about 40 – 50% of MCL are sensitive to bortezomib**, indicating that some patients possess intrinsic resistance to proteasome inhibition.

FUTURE
Targeting regulators of protein homeostasis

Inhibitors against specific E3 ligases. These ligases act on an early step in the ubiquitin-proteasome system



Proteasome Inhibitors:

-reversible: **BORTEZOMIB- FDA approved**
MLN9708 (Millennium)- phase I/II
Oprozomib ONX 0912 **(Onyx)- phase I**
Delanzomib (Cephalon) - phase III

-irreversible: Carfilzomib PR-171 (Onyx) phase III
Marizomib (Nereus)- phase Ib

Targeting the tumor ubiquitin-proteasome degradation pathway continues to be a promising strategy for human cancer therapies

Research team Therapeutic targets and new diagnostic strategies in lymphoid neoplasms

Molecular bases of apoptosis regulation induced by drugs in lymphoid neoplasms. Evaluation of new strategies for the treatment of these disorders.

Dr. Dolors Colomer
Gaël Roué
Patricia Pérez Galán
Mónica López
Laia Rosich
Sílvia Xargay
Arnau Montraveta
Sandra Moros
Alba Matas
Eriong Lee

Technicians
Jocabed Roldán
Laura Jiménez
Sandra Cabezas
Vanina Rodriguez

IDIBAPS

Institut D'Investigacions Biomèdiques August Pi i Sunyer

CLÍNIC BARCELONA Hospital Universitari

National Heart Lung and Blood Institute
People Science Health

NATIONAL INSTITUTES OF HEALTH