Molecular & Cellular Oncology 2:2, e974463; January 1, 2015; Published with license by Taylor & Francis Group, LLC

Trial Watch: Proteasomal inhibitors for anticancer therapy

Florine Obrist[1,2,3,4,†], Gwenola Manic[5,†], Guido Kroemer[2,3,6,7,8], Ilio Vitale[5,9,‡], and Lorenzo Galluzzi[2,3,4,6,‡,*]

[1]Université Paris-Sud/Paris XI; Le Kremlin-Bicêtre, France; [2]INSERM, U1138; Paris, France; [3]Equipe 11 labelisée par la Ligue Nationale contre le Cancer, Center de Recherche des Cordeliers; Paris, France; [4]Gustave Roussy Cancer Campus; Villejuif, France; [5]Regina Elena National Cancer Institute; Rome, Italy; [6]Université Paris Descartes/Paris V; Sorbonne Paris Cité; Paris, France; [7]Pôle de Biologie, Hôpital Européen Georges Pompidou; Paris, France; [8]Metabolomics and Cell Biology Platforms; Gustave Roussy Cancer Campus; Villejuif, France; [9]Department of Biology, University of Rome "Tor Vergata"

[†]These authors contributed equally to this work.
[‡]Share senior co-authorship.

Keywords: dexamethasone, immunomodulatory drugs, ixazomib, marizomib, oprozomib, rituximab

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DUB, deubiquitinase; DLBCL, diffuse large B-cell lymphoma; ER, endoplasmic reticulum; FBW7, F-box and WD repeat domain containing 7, E3 ubiquitin protein ligase; FDA, Food and Drug Administration; HDAC, histone deacetylase; HCC, hepatocellular carcinoma; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung carcinoma; RNF, ring finger protein; TCL, T-cell lymphoma; UBE2, ubiquitin-conjugating enzyme E2; UPS, ubiquitin proteasome system; USP, ubiquitin specific peptidase; WM, Waldenström's macroglobulinemia.

The so-called "ubiquitin-proteasome system" (UPS) is a multicomponent molecular apparatus that catalyzes the covalent attachment of several copies of the small protein ubiquitin to other proteins that are generally (but not always) destined to proteasomal degradation. This enzymatic cascade is crucial for the maintenance of intracellular protein homeostasis (both in physiological conditions and in the course of adaptive stress responses), and regulates a wide array of signaling pathways. In line with this notion, defects in the UPS have been associated with aging as well as with several pathological conditions including cardiac, neurodegenerative, and neoplastic disorders. As transformed cells often experience a constant state of stress (as a result of the hyperactivation of oncogenic signaling pathways and/or adverse microenvironmental conditions), their survival and proliferation are highly dependent on the integrity of the UPS. This rationale has driven an intense wave of preclinical and clinical investigation culminating in 2003 with the approval of the proteasomal inhibitor bortezomib by the US Food and Drug Administration for use in multiple myeloma patients. Another proteasomal inhibitor, carfilzomib, is now licensed by international regulatory agencies for use in multiple myeloma patients, and the approved indications for bortezomib have been extended to mantle cell lymphoma. This said, the clinical activity of bortezomib and carfilzomib is often limited by off-target effects, innate/acquired resistance, and the absence of validated predictive biomarkers. Moreover, the antineoplastic activity of proteasome inhibitors against solid tumors is poor. In this Trial Watch we discuss the contribution of the UPS to oncogenesis and tumor progression and summarize the design and/or results of recent clinical studies evaluating the therapeutic profile of proteasome inhibitors in cancer patients.

*Correspondence to: Lorenzo Galluzzi; Email: deadoc@vodafone.it; Email: iliovit@gmail.com,
Submitted: 08/03/2014; Revised: 09/15/2014; Accepted: 09/17/2014
http://dx.doi.org/10.4161/23723556.2014.974463

Introduction

The term "ubiquitin–proteasome system" (UPS) is generally used to refer to a multienzymatic machinery that mediates the physiological turnover of short-lived proteins, as well as the removal of misfolded, and hence potentially toxic, polypeptides.[1-3] This process is generally initiated by polyubiquitination, a reversible post-translational modification whereby several copies of ubiquitin, a small (76 residues, 8.5 kDa) highly-conserved polypeptide present in all eukaryotic cells, are covalently conjugated to target proteins.[4] In general terms, ubiquitination relies on 3 distinct classes of enzymes: (1) ubiquitin-activating E1 enzymes, which catalyze an ATP-dependent reaction that generates a high-energy ubiquitin–adenylate intermediate;[5] (2) ubiquitin-conjugating E2 enzymes, to which activated ubiquitin is attached to form an E2–ubiquitin thioester intermediate;[6] and (3) E3 ligases, which transfer ubiquitin from E2 intermediates to specific lysine residues on target proteins.[7] The human genome appears to encode 1-2 E1, approximately 40 E2, and more than 500 putative E3 enzymes.[8] When ubiquitination involves previously attached ubiquitin molecules (which contain several lysine residues), target proteins are tagged with multimeric ubiquitin chains, often (but not always) acting as a recognition signal for proteolytic degradation by the 26S proteasome.[9]

The 26S proteasome is a multicomponent enzymatic complex composed of 1 or 2 19S regulatory cap subunits and a central 20S catalytic core.[1,10-14] The 19S subunit is a ring-shaped particle that recognizes polyubiquitinated proteins and promotes either their ATP-dependent unfolding[3,15] or the dismantling of ubiquitin chains, a reaction catalyzed by proteasome-associated deubiquitinases (DUBs).[16-18]

The 20S subunit is a cylindrical pore consisting of 4 (2 α and 2 β) stacked rings composed of 7 subunits, 3 of which—β1, β3, and β5—are endowed with caspase-, trypsin-, and chymotrypsin-like enzymatic activities respectively. The 20S catalytic core hence mediates the nonspecific cleavage of polyubiquitinated proteins that have been unfolded by the 19S regulatory caps into small peptides and amino acids.[19-23] A detailed description of the regulation of the UPS, the pathophysiological relevance of alternative ubiquitin linkages (e.g., monoubiquitination, linear polyubiquitination), and deubiquitination reactions goes beyond the scope of this Trial Watch and can be found in several recent reviews.[1,2,6,24-36]

Besides playing a critical role in protein quality control, the UPS also regulates the abundance, enzymatic activity, and intracellular localization of several proteins involved in cellular processes as diverse as gene expression, cell cycle progression, differentiation, cell death, macroautophagy (hereafter referred to as autophagy), endocytosis, metabolic adaptation, antigen presentation, and inflammatory signaling.[24,32,37-51] Thus, the UPS resembles autophagy in that it is essential not only for the maintenance of cellular homeostasis in physiological settings, but also for adaptive responses to exogenous alterations of the intra- or extracellular microenvironment.[52-57] Underscoring the importance of the UPS for the preservation of normal cellular functions, defects in the 26S proteasome and defects in E1, E2, or E3 ligases have been associated with several human disorders, including metabolic, cardiac, autoimmune, neurodegenerative, and neoplastic processes.[27,58-62] The survival and proliferation of transformed cells, however, critically rely on an intact UPS,[63-69] possibly reflecting the phenomenon known as "non-oncogene addiction."[70,71] Indeed, the activation of oncogenic pathways and the adverse microenvironmental conditions frequently encountered by growing neoplasms render malignant cells "addicted" to gene products and molecular systems that are not tumorigenic *per se*, such as members of the heat-shock protein (HSP) family, the autophagic machinery, and the UPS.[63,67,70-74] Targeting non-oncogene addiction represents a novel therapeutic paradigm with potentially high selectivity for cancer cells, stemming from the fact that normal tissues generally do not face adverse conditions, and hence do not rely on the continued activation of adaptive stress responses.[63,67,70,71,75-77]

Today, 2 inhibitors of the 26S proteasome are approved by the US Food and Drug Administration (FDA) for use in humans: bortezomib and carfilzomib (source: http://www.fda.gov/). Bortezomib was approved for the treatment of relapsed multiple myeloma (MM) as early as in 2003[78-82] and its indications have now been extended to MM patients in general as well as to individuals with mantle cell lymphoma (MCL) who have received at least one prior therapy.[80,83,84] Carfilzomib is currently licensed for use in subjects with MM who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 d of completion of the last therapy.[80,85-88]

Milestone discoveries that have provided more precise insights into the UPS and fostered its exploitation as a target for anticancer therapy include: (1) the original description of a non-lysosomal pathway responsible for the clearance of intracellular misfolded proteins;[89] (2) the molecular characterization of the UPS as an ATP-consuming machinery that catalyzes the covalent ligation of ubiquitin to intracellular proteins for rapid proteolysis,[90-92] a discovery that earned the 2004 Nobel Prize for Chemistry to the Israeli biologist Aaron Ciechanover, the Israeli biochemist Avram Hershko, and the American biologist Irwin A. Rose;[93] (3) identification of the 26S proteasome as the multisubunit component of the UPS that recognizes and degrades polyubiquitinated proteins;[94-96] and (4) the clinical development of bortezomib.[78,79,81,97-100]

As part of our monthly Trial Watch series,[101-106] in this article we describe the impact of the UPS on oncogenesis and tumor progression, followed by a critical discussion of recent clinical trials investigating the use of proteasome inhibitors in cancer patients. Of note, the robust clinical activity of thalidomide, lenalidomide, and pomalidomide, which are collectively referred to as immunomodulatory drugs, also relies (at least in part) on inhibition of the UPS.[107,108] The clinical development of these agents has been summarized in a recent Trial Watch,[109,110] and will not be discussed further here.

Alterations of the UPS in Cancer

Accumulating evidence links alterations in the UPS to oncogenesis and tumor progression. Several E2 ligases are expressed at abnormal levels in human neoplastic tissues, including (but presumably not limited to) ubiquitin-conjugating enzyme E2Q family member 2 (UBE2Q2);[111,112] UBE2T;[113] UBE2B (also known as HR6B);[114,115] and UBE2C, an enzyme that is involved in the regulation of the metaphase–anaphase transition (also known as UBCH10).[116-119] Of note, high expression levels of UBE2C have been associated with aneuploidy and chromosome instability,[120] 2 major features of premalignant cells and malignant cells.[121-123]

Along similar lines, multiple E3 ligases are frequently overexpressed by transformed cells, including MDM2, the enzyme that targets the tumor suppressor tumor protein 53 (TP53, best known as p53) for proteasomal degradation;[124-131] HECT, UBA, and WWE domain containing 1, E3 ubiquitin protein ligase (HUWE1, also known as HECTH9), which catalyzes the ubiquitination of both *v-myc* avian myelocytomatosis viral oncogene homolog (MYC) and p53;[132-135] WW domain containing E3 ubiquitin protein ligase 1 (WWP1);[136] ring finger protein 126 (RNF126);[137] S-phase kinase-associated protein 2, E3 ubiquitin protein ligase (SKP2);[138-143] seven in absentia homologues 2 (SIAH2);[144] RNF115 (also known as BCA2);[145] and E6, a viral E3 ligase expressed by variants of the human papillomavirus that is associated with nasopharyngeal and cervical

carcinomas[146-148] and exerts tumorigenic effects by promoting the degradation of p53.[149-151] In addition, several E3 ligases are lost or affected by loss-of-function mutations in the course of tumorigenesis and tumor progression, including speckle-type POZ protein (SPOP);[152] breast cancer 1, early onset (BRCA1), which is critically involved in transcription and DNA repair;[153-156] von Hippel-Lindau tumor suppressor, E3 ubiquitin protein ligase (VHL);[157] and F-box and WD repeat domain containing 7, E3 ubiquitin protein ligase (FBW7), which is involved in the degradation of substrates relevant for cell growth, proliferation, and apoptosis.[158-161] Similar to the overexpression of UBE2C, loss-of-function FBW7 mutations have been associated with an oncogenic phenotype characterized by high degrees of chromosomal instability.[159,160]

In addition, proteasomal subunits and DUBs can exhibit quantitative or functional alterations in cancer cells. This is the case for proteasome (prosome, macropain) 26S subunit, ATPase, 2 (PSMC2);[69,162] cylindromatosis (CYLD), a tumor suppressor protein involved in NF-κB signaling and regulated variants of necrosis;[163-167] ubiquitin specific peptidase 1 (USP1);[168] USP2A, the DUB that operates on MDM2 and cyclin D1;[169-172] USP9X, whose upregulation correlates with increased levels of the antiapoptotic Bcl−2 family member myeloid cell leukemia 1 (MCL1);[39,173,174] and USP28.[175]

In these settings, defects in the UPS appear to contribute to oncogenesis and tumor progression by altering the proper turnover of oncoproteins and tumor suppressor proteins, hence (1) affecting key cellular processes including (but not limited to) cell cycle progression,[137-143] differentiation,[159] and regulated variants of cell death;[158,163,173,176] (2) favoring genomic instability and/or aneuploidy;[120,159,160] and (3) increasing the resistance of cancer cells to antineoplastic agents.[136,177]

Targeting the 26S proteasome as an anticancer intervention

Throughout the past 3 decades the effect of chemical UPS inhibitors on the survival and proliferation of cancer cells has been the subject of an intense wave of investigation, resulting in an abundant scientific literature. Most of these studies originated from the hypothesis that neoplastic cells have an increased demand for protein degradation and therefore rely on proteasomal functions to a greater extent than their non-transformed counterparts.[63-66] This is presumably a consequence of the malignant phenotype itself, which is associated with severe proteotoxic stress,[66,178–180] and the adverse microenvironmental conditions frequently encountered by cancer cells.[66,178-183] In this context, three categories of compounds that have been shown to block the proteolytic activity of the 26S proteasome at the level of the 20S subunit have been, or are being, developed in the clinic: (1) boronate-based agents, encompassing bortezomib, delanzomib, and ixazomib; (2) peptide epoxyketone-based agents, such as carfilzomib and oprozomib; and (3) non-peptide β-lactone-based chemicals, including marizomib.[80,184]

The antineoplastic activity of proteasome inhibitors is multifactorial and exhibits at least some degree of context dependency. Thus, the blockade of proteasomal protein degradation may exert cytostatic[185-189] or cytotoxic[185,190-192] effects upon inhibition of the NF-κB signaling pathway,[193-196] overproduction of reactive oxygen species (ROS),[186,197-199] and activation of the mitogen-activated protein kinase 8 (MAPK8, best known as JNK1) and p53 signaling.[200] Proteasome inhibitors have also been shown to provoke endoplasmic reticulum (ER) stress by abrogating ER-associated protein degradation,[201-204] *de facto* favoring the accumulation of misfolded or polyubiquitinated (and potentially toxic) proteins and impairing mitochondrial functions.[202,205] In line with this notion, bortezomib efficiently triggers an immunogenic variant of apoptosis that critically relies on the establishment of ER stress.[206-209] At least in part, the ability of bortezomib to kill cancer cells while promoting the establishment of a tumor-specific immune response may explain its clinical success in MM patients.[51,210-212]

Bortezomib

As mentioned above, bortezomib (also known as PS341 or Velcade®) is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome.[213-216] This boronate-based agent has been reported to mediate robust antineoplastic effects against a variety of human cancer cell lines *in vitro* and *in vivo*.[217-220] This said, the sensitivity of malignant cells to bortezomib varies considerably among cancer cells of distinct histologic origin or that exhibit different oncogenic alterations.[221,222] However, a large amount of preclinical data that accumulated in the early 2000s indicates that bortezomib is particularly efficient against otherwise chemoresistant hematologic malignancies, including MM.[220,223-226]

Completed clinical studies

In the past decade, dozens of studies have investigated the therapeutic profile of bortezomib in individuals with relapsed refractory MM (**Table 1**). The safety and antineoplastic activity demonstrated by bortezomib in initial Phase I-II trials[78,79,97,227-229] drove the primary approval of this drug by the US FDA for use in MM patients who failed to benefit from at least 2 lines of previous therapy. Indeed, MM patients receiving bortezomib exhibited a response rate of approximately 37% (~27% partial responses, ~10% complete or near-to-complete responses) and a median overall survival of 16 mo.[79] Subsequent clinical trials demonstrated the superior anticancer activity of (1) bortezomib monotherapy compared to high-dose dexamethasone (an FDA-approved glucocorticosteroid that exerts cytotoxic effects against several hematologic malignancies)[230-233] in subjects with relapsed or refractory MM;[98,234] and (2) bortezomib combined with prednisone (another glucocorticosteroid licensed for use in cancer patients)[81,235] and melphalan (an alkylating agent currently employed for the treatment of MM, ovarian carcinoma, and melanoma)[236] compared to melphalan plus prednisone in patients with newly diagnosed MM who were ineligible for high-dose chemotherapy.[237-246] Bortezomib employed as a stand-alone therapeutic intervention has also been associated with a good clinical profile (toxicity, response rate, and duration of response) in subjects with relapsed or refractory MCL,[83,84] and in patients with recurrent or refractory follicular lymphoma.[247,248] These data underpinned the approval of bortezomib for use in MCL

Table 1. Completed clinical trials testing the therapeutic profile of bortezomib in cancer patients.

Indication(s)	Phase	Notes	Ref.
Biliary tract cancers	II	As single agent	326
Breast cancer	II	Combined with doxorubicine	331
Follicular lymphoma	II	As single agent	247
		Combined with bendamustine and rituximab	307
Gastric or gastroesophageal carcinoma	I	Combined with epirubicin, carboplatin and capecitabine	315
	II	As single agent	324
Glioblastoma multiforme	II	Combined with vorinostat	329
Hepatocellular carcinoma	II	As single agent	325
		Combined with doxorubicine	333
Head and neck cancer	I	Combined with cisplatin-based chemoradiotherapy	318
	II	As single agent or combined with irinotecan	328
		Combined with doxorubicine	327
Hematologic neoplasms	I	Combined with doxorubicin	264
	I/II	Combined with chemotherapy and HSCT	311
		Combined with gemcitabine	312
		Combined with R-CHOP	308
Melanoma and soft tissue sarcoma	I	Combined with dacarbazine	321
Mesothelioma	II	Combined with cisplatin	330
Mantle cell lymphoma	II	As single agent	83,84
		Combined with gemcitabine	297
Myelodysplastic syndrome	I/II	Combined with cytarabine	300
	I	As single agent	227–229
	Ib	Combined with panobinostat and dexamethasone	269
	I/II	Combined with bendamustine, rituximab and dexamethasone	286
		Combined with doxorubicin and dexamethasone	266
		Combined with fotemustine and dexamethasone	292
		Combined with melphalan and prednisone	241,243
	II	As single agent	78,79,97,251
		Combined with bendamustine and rituximab	284,285
		Combined with bevacizumab	287
		Combined with dexamethasone	252,254
		Combined with dexamethasone and DLIs	255
		Combined with doxorubicin	263
		Combined with doxorubicin and dexamethasone	265,267
		Combined with fludarabine and melphalan prior to HSCT	295
		Combined with lenalidomide and dexamethasone	278
		Combined with melphalan, lenalidomide, and HSCT	296.
		Combined with melphalan, prednisone, and siltuximab	239
		Combined with panobinostat and dexamethasone	270
		Combined with thalidomide, dexamethasone, and cyclophosphamide	277
	III	As single agent	98,234
		Combined with melphalan and prednisone	237,238,240,242
		Combined with melphalan- and prednisone-based chemotherapy	240,245
		Combined with melphalan and prednisone or thalidomide and prednisone	240,244,246
		Combined with thalidomide and dexamethasone	276
		Combined with vorinostat	268
	IIIb	As single agent or combined with dexamethasone	253
Non-Hodgkin's lymphoma	I	Combined with ^{90}Y-ibritumomab tiuxetan	303
	II	Combined with rituximab and dexamethasone	306
Non-small cell lung carcinoma	I	Combined with vorinostat and consolidative surgery	322
	II	As single agent	323
		Combined with vorinostat	332
Ovarian carcinoma	II	Combined with doxorubicine	337
Prostate carcinoma	II	Combined with prednisone	334
		Combined with docetaxel	336
Advanced solid tumors	I	Combined with oxaliplatin	320
		Combined with sorafenib	314
		Combined with sunitinib	317
		Combined with tanespimycin	316
		Combined with vorinostat	313,319

Abbreviations: DLI, donor lymphocyte infusion; HSCT, hematopoietic stem cell transplantation; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

patients who have received at least one prior therapy.[80,213] Common toxicities associated with the use of bortezomib as a single agent in individuals affected by MM and MCL include gastrointestinal disorders, anemia, thrombocytopenia, fatigue, and peripheral neuropathy.[80,229,249-251]

Bortezomib has also been demonstrated to boost the therapeutic activity of multiple chemotherapeutic agents in MM patients (**Table 1**), including (1) dexamethasone, employed as a stand-alone therapeutic intervention or followed by donor lymphocyte infusions upon allogeneic stem cell transplantation;[252-259] (2) doxorubicin (an immunogenic anthracycline approved by the FDA for the treatment of various hematologic and solid malignancies),[103,260-262] alone or combined with dexamethasone;[263-267] (3) histone deacetylase (HDAC) inhibitors;[268-272] (4) thalidomide (an immunomodulatory drug licensed for use in MM patients),[110] combined with cyclophosphamide (an immunogenic alkylating agent currently approved for the treatment of multiple neoplasms)[273-275] and/or dexamethasone;[276,277] (5) lenalidomide plus dexamethasone (an immunomodulatory chemotherapeutic regimen approved for the treatment of MM, MCL, and myelodysplastic syndromes [MDSs]);[278,279] (6) bendamustine (an alkylating agent currently employed for chronic lymphocytic leukemia [CLL] and non-Hodgkin's lymphoma [NHL]),[280-282] in combination with rituximab (a monoclonal antibody targeting CD20 licensed for the treatment of CLL and NHL)[104,283] and/or dexamethasone;[284-286] (7) bevacizumab (a monoclonal antibody targeting the vascular endothelial growth factor [VEGF] that is currently approved for the treatment of several neoplasms);[287-289] (8) fotemustine (another alkylating agent currently approved for use in melanoma patients)[290,291] and dexamethasone;[292] (9) fludarabine (a nucleoside analog used for the treatment of CLL)[293,294] plus melphalan, used as a conditioning regimen before allogeneic stem cell transplantation;[295] and (10) intermediate-dose melphalan and autologous stem cell transplantation, followed by lenalidomide-based consolidation.[296]

Of note, bortezomib-based chemotherapeutic cocktails exert anticancer effects not only in MM patients, but also in subjects bearing other hematologic neoplasms. These include: (1) MCL patients receiving bortezomib plus gemcitabine (an immunostimulatory nucleoside analog used for the treatment of distinct solid malignancies);[297-299] (2) individuals with high-risk MDS treated with bortezomib combined with low-dose cytarabine (a nucleoside analog used for the treatment of different types of leukemia);[300-302] (3) NHL patients receiving bortezomib in combination with the FDA-approved CD20-targeting monoclonal antibody ^{90}Y-ibritumomab tiuxetan[303-305] or with rituximab plus low-dose dexamethasone;[306] (4) subjects with relapsed or refractory follicular lymphoma treated with bortezomib plus bendamustine and rituximab;[307] (5) diffuse large B-cell lymphoma (DLBCL) and MCL patients receiving bortezomib in the context of a rituximab- cyclophosphamide-, doxorubicin-, vincristine-, and prednisone-based chemotherapeutic combination commonly known as R-CHOP;[308] (6) NHL and MCL patients treated with bortezomib plus etoposide (an FDA-approved inhibitor of topoisomerase II commonly used for the treatment of several neoplasms),[309,310] cytarabine, melphalan, and autologous hematopoietic stem cell transplantation;[311] (7) subjects with refractory DLBCL or peripheral T-cell lymphoma (TCL) receiving bortezomib plus gemcitabine.[312]

The results of some Phase I clinical trials (mainly investigating safety, tolerability, and dosing schedules) supported the development of bortezomib in combination with other therapeutic interventions for the treatment of some solid malignancies.[313-322] Nonetheless, the findings of Phase II trials performed so far are quite disappointing. Although well tolerated, bortezomib monotherapy displays limited, if any, clinical activity against chemotherapy-naïve, metastatic non-small cell lung carcinoma (NSCLC),[323] advanced gastric or gastroesophageal junction adenocarcinoma,[324] unresectable hepatocellular carcinoma (HCC),[325] and advanced tumors of the biliary tract.[326] Along similar lines, various bortezomib-based chemotherapeutic cocktails have been shown to mediate negligible antineoplastic effects in patients with head and neck tumors,[327,328] recurrent glioblastoma,[329] malignant pleural mesothelioma,[330] metastatic breast carcinoma,[331] advanced NSCLC,[332] HCC,[333] castration-resistant metastatic prostate cancer,[334-336] and ovarian carcinoma.[337]

Together, these observations suggest that bortezomib, alone or combined with other chemotherapeutic interventions, mediates significant therapeutic benefits exclusively in patients affected by hematologic malignancies. Interestingly, the elevated sensitivity of MM to bortezomib has been ascribed to the fact that MM cells (*de facto* originating from plasma cells) produce high titers of abnormal immunoglobulins and hence critically rely on the activity of the so-called immunoproteasome, a bortezomib-sensitive variant of the 26S proteasome that is upregulated in response to inflammatory cytokines.[338-341] In this setting, the relatively low efficiency of bortezomib at the molecular level (bortezomib is estimated to reduce the global proteolytic activity of the 26S proteasome by 20–30%)[342] may be sufficient to efficiently kill transformed cells.

Ongoing clinical trials

Official sources list 15 ongoing (not terminated, withdrawn, suspended, or completed) clinical trials launched after January 1 2012 that are aimed at assessing the safety and antineoplastic activity of bortezomib as an off-label therapeutic intervention, i.e., in patients affected by malignancies other than MM and MCL (http://www.clinicaltrials.gov/) (**Table 2**). In particular, bortezomib is being tested in individuals with: (1) relapsed or refractory acute lymphoblastic leukemia (ALL), in combination with doxorubicin, dexamethasone, vincristine (a microtubular poison currently licensed for the treatment of several malignancies),[343-345] and pegylated asparaginase (a recombinant enzyme commonly employed for this oncologic indication) (NCT01769209); (2) acute myeloid leukemia (AML), in combination with arsenic trioxide (NCT01950611), sorafenib (a FDA-approved multikinase inhibitor)[346-348] and decitabine (a nucleoside analog employed for the treatment of AML and MDS)[301,349] (NCT01861314), liposomal doxorubicin (NCT01736943), or sorafenib plus the HDAC inhibitor

Table 2. Ongoing clinical trials recently launched to evaluate the safety and efficacy of off-label bortezomib in cancer patients.*

Indication(s)	Phase	Status	Notes	Ref.
Acute lymphoblastic leukemia	II	Recruiting	Combined with doxorubicin-based radiotherapy	NCT01769209
Acute myeloid leukemia	I	Recruiting	Combined with decitabine and sorafenib	NCT01861314
	I/II	Recruiting	Combined with sorafenib and vorinostat	NCT01534260
	II	Recruiting	Combined with arsenic trioxide	NCT01950611
			Combined with liposomal doxorubicin	NCT01736943
Diffuse large B-cell lymphoma	II	Recruiting	As single agent	NCT01965977
			Combined with rituximab, cyclophosphamide, doxorubicin, and prednisone	NCT01848132
	II/III	Recruiting	Combined with rituximab-based chemotherapy prior to HSCT	NCT01805557
Hematologic neoplasms	I	Recruiting	Combined with alisertib and rituximab	NCT01695941
	III	Not yet recruiting	Combined with cyclophosphamide- and doxorubicin-based chemoradiotherapy	NCT02112916
Myelodysplastic syndrome	II	Recruiting	As single agent	NCT01891968
Neuroblastoma	I/II	Recruiting	Combined with eflornithine	NCT02139397
Non-small cell lung carcinoma	II	Recruiting	Combined with acyclovir	NCT01833143
Waldenström's macroglobulinemia	II	Recruiting	Combined with cyclophosphamide, dexamethasone, and rituximab	NCT01788020
	III	Recruiting	Combined with cyclophosphamide, fludarabine, and rituximab	NCT01592981

Abbreviation: HSCT, hematopoietic stem cell transplantation.
*initiated after January 1 2012 and not terminated, suspended, withdrawn, or completed at the date of submission.

vorinostat[350] (NCT01534260); (3) DLBCL, either as a stand-alone maintenance therapy (NCT01902862), or as an induction therapy in combination with rituximab, dexamethasone, cytarabine, and cisplatin (a platinum derivative commonly employed against several solid neoplasms)[351-354] prior to high-dose chemotherapy and autologous stem cell transplantation (NCT01805557), or combined with rituximab, cyclophosphamide, doxorubicin, and prednisone (NCT01848132); (4) low- or intermediate-risk MDS, as a single agent (NCT01891968); (5) Waldenström's macroglobulinemia (WM), combined with cyclophosphamide, rituximab and dexamethasone (NCT01788020) or with cyclophosphamide, rituximab, and fludarabine (NCT01592981); and (6) various hematologic malignancies, in combination with the experimental inhibitor of aurora kinase A (AURKA) alisertib and rituximab (NCT01695941) or a multicomponent chemotherapeutic cocktail (NCT02112916). Moreover, the therapeutic potential of bortezomib is being investigated in subjects with relapsed or refractory neuroblastoma, who receive it in combination with the ornithine decarboxylase inhibitor eflornithine (which is currently approved as a topical intervention against facial hirsutism and as a systemic treatment for sleeping sickness)[355-358] (NCT02139397), and in NSCLC patients bearing *KRAS* mutations or with a limited smoking history, who are treated with bortezomib plus acyclovir (a guanosine analog currently approved for the treatment of herpes simplex virus infection)[359-362] (NCT01833143).

Carfilzomib

Several MM patients either do not respond or become refractory to bortezomib monotherapy.[363-365] A variety of molecular alterations have been proved to contribute to such innate or acquired resistance, including overexpression of wild-type or mutant proteasome components;[366-370] constitutive activation of NF-κB[371,372] or insulin-like growth factor 1 receptor (IGF1R)[373,374] signaling; a block in mitochondrial apoptosis;[375] upregulation of the chaperones involved in the ER unfolded protein response;[376] increased expression levels of multidrug transporters;[377-379] and the elicitation of nuclear factor, erythroid 2-like 2 (NFE2L2)-dependent responses to oxidative stress.[380] This has driven the development of carfilzomib (also known as PR-171), a second-generation, epoxyketone-based, irreversible inhibitor of the chymotrypsin-like activity of the 26S proteasome.[381-383] Carfilzomib rapidly turned out to mediate robust antineoplastic effects against several hematologic malignancies (including MM) *in vitro* and *in vivo*.[381-383] Similar to that of bortezomib, the pronounced antimyeloma activity of carfilzomib has been attributed to its ability to inhibit the immunoproteasome.[383]

Completed clinical studies

The safety profile and efficacy of carfilzomib monotherapy in MM patients have been demonstrated by several clinical studies, including 2 Phase I[384,385] and 4 open-label, single-arm Phase 2[85-88] trials (**Table 3**). In one of these studies, carfilzomib was associated with durable clinical responses (overall response rate 23.7%, median duration of response 7.8 mo, median overall survival 15.6 mo) and an acceptable toxicity profile,[87] supporting approval of this agent by the FDA for the treatment of relapsed and refractory MM patients who have received at least 2 prior therapies, including bortezomib.[386] Importantly, a prospective analysis performed on this patient cohort revealed that single-agent carfilzomib has the potential to at least partially overcome the impact of high-risk cytogenetics in heavily pretreated MM patients.[387] Moreover, carfilzomib appears to be associated with a reduced incidence of peripheral neuropathy (13.9%).[388] The combination of carfilzomib with lenalidomide and dexamethasone also seems to be well tolerated and to promote robust, rapid, and durable responses in patients with both relapsed/progressive[389,390] and newly diagnosed[391] MM. In particular, 62% of individuals with newly diagnosed MM achieved at least a near-complete clinical response in response to this chemotherapeutic cocktail, with a 2-y progression-free survival estimate of 92%.[391] Recently, an open-label, intra-patient Phase I/II clinical trial

Table 3. Completed clinical trials testing the therapeutic profile of carfilzomib in cancer patients.

Indication(s)	Phase	Notes	Ref.
Multiple myeloma	I	As single agent	384,385
	Ib	Combined with dexamethasone and lenalidomide	389
	I/II	Combined with a panel of chemotherapeutics	392
		Combined with dexamethasone and lenalidomide	391
	II	As single agent	85–88,387
		Combined with dexamethasone and lenalidomide	390
		Combined with dexamethasone and cyclophosphamide	393
	III	As single agent	394
Advanced solid tumors	I/II	As single agent	395

demonstrated that replacing bortezomib with carfilzomib is safe and can provide therapeutic benefits to MM patients who are progressing on bortezomib-based combinatorial chemotherapy.[392] Moreover, the results of a Phase II study indicate that combining carfilzomib with cyclophosphamide and dexamethasone is associated with a good safety profile and high rates of complete response among patients with newly diagnosed MM.[393] A randomized, open-label Phase III study is currently ongoing to compare the overall survival of carfilzomib monotherapy to best supportive care in relapsed or refractory MM patients.[394] Of note, similar to bortezomib, carfilzomib is well tolerated by patients with advanced solid tumors but exerts limited, if any, antineoplastic activity.[395]

Ongoing clinical trials

Official sources list 14 ongoing (not terminated, withdrawn, suspended, or completed) clinical trials launched after January 1 2012 to investigate the therapeutic profile of carfilzomib as an off-label therapeutic intervention, i.e., in patients affected by neoplasms other than MM (http://www.clinicaltrials.gov/) (**Table 4**). Carfilzomib is being evaluated as a stand-alone therapeutic intervention in patients with (1) relapsed or refractory MCL (NCT02042950); (2) refractory renal cell carcinoma (NCT01775930); or (3) advanced malignancies (NCT01949545). Moreover, the safety and efficacy of carfilzomib are being tested in (1) patients with relapsed or refractory DLBCL, receiving carfilzomib in the context of rituximab-based chemotherapy (NCT01959698; NCT02073097); (2) subjects with relapsed or refractory MCL, who are treated with carfilzomib plus lenalidomide and rituximab (NCT01729104); (3) patients with relapsed or refractory NHL, receiving carfilzomib in combination with an FDA-approved histone deacetylase inhibitor (belinostat)[271,396-398] (NCT02142530) or bendamustine and rituximab (NCT02187133); (4) patients with relapsed WM, with carfilzomib, rituximab, and dexamethasone (NCT01813227); (5) subjects with cutaneous TCL, receiving carfilzomib plus the FDA-approved HDAC inhibitor romidepsin[397-400] (NCT01738594); and (6) MCL, TCL, and DLBCL patients, who are treated with carfilzomib and dexamethasone as consolidation therapy after autologous stem cell transplantation (NCT01926665). Finally, the clinical profile of carfilzomib is being assessed in (1) previously untreated subjects affected by extensive stage small-cell lung cancer, who are treated with carfilzomib plus carboplatin (a platinum derivative employed for the treatment of multiple solid tumors, including ovarian carcinoma)[401-403] and etoposide (NCT01987232); (2) subjects with relapsed lung cancer, receiving carfilzomib in combination with irinotecan (a topoisomerase I inhibitor mainly used for the treatment of colorectal carcinoma)[404,405] (NCT01941316);

Table 4. Ongoing clinical trials recently launched to evaluate the safety and efficacy of off-label carfilzomib in cancer patients.*

Indication(s)	Phase	Status	Notes	Ref.
Diffuse large B-cell lymphoma	I/II	Not yet recruiting	Combined with rituximab and CHOP	NCT02073097
		Recruiting	Combined with rituximab, ifosfamide, carboplatin, and etoposide	NCT01959698
Hematological neoplasms	I	Recruiting	Combined with dexamethasone and HSCT	NCT01926665
Mantle cell lymphoma	I/II	Recruiting	Combined with lenalidomide and rituximab	NCT01729104
	II	Not yet recruiting	As single agent	NCT02042950
Non-Hodgkin's lymphoma	I	Not yet recruiting	Combined with belinostat	NCT02142530
			Combined with bendamustine and rituximab	NCT02187133
Prostate carcinoma	II	Recruiting	Combined with dexamethasone and acyclovir	NCT02047253
Renal cell carcinoma	II	Active, not recruiting	As single agent	NCT01775930
Small cell lung carcinoma	I/II	Recruiting	Combined with carboplatin and etoposide	NCT01987232
T-cell lymphoma	I	Recruiting	Combined with romidepsin	NCT01738594
Waldenström's macroglobulinemia	II	Recruiting	Combined with dexamethasone and rituximab	NCT01813227
Advanced tumors	I	Recruiting	As single agent	NCT01949545
	I/II	Recruiting	Combined with irinotecan	NCT01941316

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HSCT, hematopoietic stem cell transplantation.
*initiated after January 1 2012 and not terminated, suspended, withdrawn, or completed at the date of submission.

and (3) patients with metastatic castration-resistant prostate cancer,[335] who are treated with carfilzomib, dexamethasone, and acyclovir (NCT02047253).

Additional proteasome inhibitors

Other clinically relevant inhibitors of the 26S proteasome include: (1) marizomib (also known as NPI-0052), an irreversible inhibitor of both the chymotrypsin- and trypsin-like enzymatic activities of the 20S subunit[406-410] that exhibits improved bioavailability compared to bortezomib and carfilzomib, perhaps because of its non-peptidic nature,[411] and robust antineoplastic activity in preclinical models;[190,412-415] ixazomib (also known as MLN9708), a boronate-based agent characterized by increased oral availability and antitumor activity compared to bortezomib;[184,416] (3) oprozomib (also known as ONX-0912), a carfilzomib-like orally bioavailable inhibitor of the chymotrypsin-like activity of the 20S subunit,[417,418] which is active against MM and head and neck cancers;[419,420] and (4) delanzomib (also known as CEP-18770), a potent, reversible, and orally bioavailable agent[421-424] exhibiting high antineoplastic activity in preclinical models of MM both as monotherapy[425] and in combination with other chemotherapeutic agents.[425,426] Intriguingly, some of these chemicals, including marizomib, have been reported to synergize with bortezomib in the killing of MM cells,[409,427] suggesting that the mechanisms of action of distinct proteasome inhibitors may not be completely overlapping.

Clinical studies

Marizomib-based monotherapy has been associated with a promising safety profile (no evidence of thrombocytopenia and peripheral neuropathy) and clinical efficacy in Phase I trials enrolling relapsed and refractory MM patients.[80,407,411,428] In addition, the combination of marizomib and vorinostat was well tolerated by patients with advanced solid tumors.[429] According to official sources (http://www.clinicaltrials.gov/, ongoing trials initiated after January 1 2012), the safety and antineoplastic activity of marizomib are currently being assessed in relapsed or refractory MM patients, receiving marizomib either as a standalone therapeutic intervention (NCT00461045) or in combination with pomalidomide (an immunomodulatory agent approved by the US FDA for the treatment of MM)[110,430-433] and low-dose dexamethasone (NCT02103335) (**Table 5**).

The safety and tolerability of ixazomib have been evaluated in several Phase I clinical trials enrolling subjects with relapsed/refractory MM.[434-440] In 2 of these studies, 15–18% of patients were reported to achieve at least a partial response to therapy,[434,435] supporting further clinical development. Along similar lines, ixazomib (co-administered with dexamethasone and lenalidomide) was well tolerated by individuals with previously

Table 5. Clinical trials recently launched to evaluate the safety and efficacy of third-generation proteasomal inhibitors in cancer patients.*

Inhibitor	Indication(s)	Phase	Status	Notes	Ref.
Ixazomib	Acute myeloid leukemia	I	Not yet recruiting	Combined with cytarabine, etoposide, and mitoxantrone	NCT02070458
		II	Recruiting	As single agent	NCT02030405
	Follicular lymphoma	II	Recruiting	As single agent	NCT01939899
	Hematologic neoplasms	I	Recruiting	Combined with doxorubicin-based chemotherapy	NCT01887587
		II	Not yet recruiting	As single agent after HSCT	NCT02169791
	Multiple myeloma	I	Recruiting	Combined with dexamethasone and lenalidomide	NCT01645930
				Combined with dexamethasone	NCT01830816
				Combined with dexamethasone and panobinostat	NCT02057640
		I/II	Not yet recruiting	Combined with dexamethasone and pomalidomide	NCT02119468
			Recruiting	Combined with dexamethasone and cyclophosphamide	NCT01864018
				Combined with dexamethasone and pomalidomide	NCT02004275
		II	Not yet recruiting	As single agent after HSCT	NCT02168101
				Combined with dexamethasone and lenalidomide	NCT01936532
			Recruiting	Combined with dexamethasone	NCT01415882
				Combined with lenalidomide after HSCT	NCT01718743
				Combined with dexamethasone and cyclophosphamide	NCT02046070
		III	Not yet recruiting	As single agent after HSCT	NCT02181413
		III	Recruiting	Combined with dexamethasone and lenalidomide	NCT01564537
					NCT01850524
	T-cell lymphoma	II	Not yet recruiting	As single agent	NCT02158975
	Advanced tumors	I	Not yet recruiting	Combined with vorinostat	NCT02042989
			Recruiting	As single agent	NCT01912222
					NCT01953783
Marizomib	Multiple myeloma	I	Recruiting	Combined with dexamethasone and pomalidomide	NCT02103335
		I/II	Recruiting	As single agent	NCT00461045
Oprozomib	Multiple myeloma	I/II	Recruiting	Combined with dexamethasone and lenalidomide or cyclophosphamide	NCT01881789
				Combined with dexamethasone	NCT01832727
				Combined with dexamethasone and pomalidomide	NCT01999335
				Combined with melphalan and prednisone	NCT02072863

Abbreviations: HSCT, hematopoietic stem cell transplantation.
*initiated after January 1 2012 and not terminated, suspended, withdrawn, or completed at the date of submission.

untreated MM and exerted some degree of clinical activity.[441,442] According to official sources, no fewer than 14 clinical trials have been initiated after January 1 2012 to evaluate the therapeutic potential of ixazomib in subjects with hematologic malignancies (http://www.clinicaltrials.gov/). In these studies, ixazomib is being tested (1) as a single agent for post-transplantation maintenance in patients with MM (NCT02168101; NCT02181413) or various hematologic tumors including MM (NCT02169791); (2) in combination with dexamethasone for relapsed and refractory (NCT01830816) or relapsed but not refractory (NCT01415882) MM; (3) in combination with dexamethasone and cyclophosphamide in newly-diagnosed MM patients (NCT01864018, NCT02046070); (4) in combination with dexamethasone and panobinostat (an experimental non-selective HDAC inhibitor)[397,398] in subjects with relapsed and/or refractory MM (NCT02057640); (5) in combination with dexamethasone and pomalidomide in refractory (NCT02004275) or relapsed/refractory (NCT02119468) MM patients; (6) with lenalidomide only, as a maintenance regimen upon autologous stem cell transplantation in MM patients (NCT01718743); (7) with lenalidomide and dexamethasone, in patients with either newly diagnosed (NCT01850524, NCT01936532) or relapsed/refractory (NCT01564537, NCT01645930) MM. Moreover, ixazomib monotherapy is being evaluated in non-MM patients, including (1) subjects with relapsed or refractory AML (NCT02030405); (2) individuals with relapsed/refractory cutaneous and peripheral TCL (NCT02158975); (3) patients with relapsed/refractory follicular lymphoma (NCT01939899); (4) subjects with hematologic malignancies or advanced solid tumors (NCT01912222); and (5) individuals with lymphomas or advanced solid tumors (NCT01953783). Finally, ixazomib is being assessed in combination with (1) mitoxantrone (an FDA-approved immunogenic anthracycline used for the therapy of NHL, AML, and breast carcinoma),[443-446] etoposide, and intermediate-dose cytarabine in relapsed/refractory AML patients (NCT02070458); (2) vincristine, doxorubicin, pegylated-asparaginase, and dexamethasone in subjects with relapsed/refractory ALL or lymphoma (NCT01887587); and (3) vorinostat, in individuals with advanced solid tumors (NCT02042989) (**Table 5**).

The safety and tolerability of oprozomib have been evaluated in Phase I studies performed on patients with hematologic malignancies and advanced solid tumors.[447,448] According to official sources (http://www.clinicaltrials.gov/, ongoing trials initiated after January 1 2012), the clinical profile of oprozomib is being investigated in (1) transplant-ineligible patients with newly diagnosed MM, receiving oprozomib plus dexamethasone and lenalidomide (NCT01881789), or dexamethasone and oral cyclophosphamide (NCT01881789), or prednisone and melphalan (NCT02072863), (2) relapsed and/or refractory MM patients, treated with oprozomib plus dexamethasone (NCT01832727); and (3) subjects with primary refractory or relapsed/refractory MM, receiving oprozomib with pomalidomide and dexamethasone (NCT01999335) (**Table 5**).

Finally, results from a relatively recent Phase I clinical trial enrolling patients with advanced solid tumors and MM demonstrated a favorable safety profile for delanzomib, which in this setting was not associated with significant neurotoxicity and skin toxicity.[449] The clinical development of this proteasome inhibitor has nonetheless been discontinued due to a lack of efficacy documented in a Phase I/II trial conducted on relapsed refractory MM patients.[411,450]

Concluding Remarks

The clinical advantages provided by proteasome inhibitors to MM patients have been demonstrated by a large number of clinical studies. However, bortezomib, carfilzomib, and similar agents generally lack therapeutic activity against solid tumors. In addition, the clinical activity of proteasome inhibitors in MM patients can be limited by (1) side effects, including thrombocytopenia and peripheral neuropathy,[251,451-456] that call for reductions in dosage or the discontinuation of therapy[251] and often result in poor therapeutic effects;[78,97,98,254,457,458] (2) innate or acquired resistance;[363-365] and (3) the absence of validated predictive biomarkers that allow preselection of patients who have a high chance of truly benefitting from therapy.[64,459,460] Modifications in drug administration protocols (e.g., alternative routes),[461], the implementation of novel combinatorial chemotherapeutic regimens, and the development of third-generation proteasome inhibitors with improved bioavailability and reduced toxicity may broaden the therapeutic utility of these compounds against hematologic malignancies and solid tumors. As an alternative, therapeutic strategies targeting other components of the UPS and DUBs have been proposed. Although such an approach holds promise, only a few compounds such as MDM2 antagonists (e.g., nutlin-3, serdemetan) and NEDD8-activating enzyme (NAE) inhibitors (e.g., MLN4924) have entered clinical development to date.[462,463]

Accumulating evidence indicates that regulation of the UPS in both physiologic and pathologic settings is more complex than originally thought, which complicates the development of clinically useful proteasome targeting agents[64,464] Moreover, limiting proteasomal protein degradation in healthy tissues may favor tumorigenesis (by stabilizing oncoproteins or inhibiting tumor suppressors) and/or neurodegenerative disorders (by promoting the accumulation of potentially neurotoxic misfolded proteins).[64,464] Along similar lines, the UPS plays a critical role in the processing of intracellular proteins for antigen presentation,[32,50,465-468] implying that proteasome inhibitors may negatively affect the elicitation of therapeutically relevant anticancer immune responses.

An improved understanding of the composition, function, and regulation of the UPS, as well as the molecular mechanisms underlying the intrinsic or acquired resistance of some neoplasms to proteasome-targeting agents, may pave the way to the design of novel effective anticancer chemotherapies based on proteasome inhibition and to their successful translation from the bench to the bedside.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Funding

Authors are supported by the European Commission (ArtForce); Agence National de la Recherche (ANR); Associazione Italiana per la Ricerca sul Cancro (AIRC: *MFAG 2013 #14641 and triennial tellowship "Antonietta Latronico", 2014*); Italian Ministry of Health (GR-2011-02351355); Programma per i Giovani Ricercatori "Rita Levi Montalcini" 2011; Ligue Nationale contre le Cancer; Fondation pour la Recherche Médicale (FRM); Institut National du Cancer (INCa); Association pour la Recherche sur le Cancer (ARC), LabEx Immuno-Oncologie; Fondation de France; Fondation Bettencourt-Schueller; AXA Chair for Longevity Research; Cancéropôle Ile-de-France, Paris Alliance of Cancer Research Institutes (PACRI) and Cancer Research for Personalized Medicine (CARPEM).

References

1. Bhattacharyya S, Yu H, Mim C, Matouschek A. Regulated protein turnover: snapshots of the proteasome in action. Nat Rev Mol Cell Biol 2014; 15:122-33; PMID:24452470; http://dx.doi.org/10.1038/nrm3741
2. Kleiger G, Mayor T. Perilous journey: a tour of the ubiquitin-proteasome system. Trends Cell Biol 2014; 24:352-9; PMID:24457024; http://dx.doi.org/10.1016/j.tcb.2013.12.003
3. Finley D. Recognition and processing of ubiquitin-protein conjugates by the proteasome. Annu Rev Biochem 2009; 78:477-513; PMID:19489727; http://dx.doi.org/10.1146/annurev.biochem.78.081507.101607
4. Wilkinson KD. The discovery of ubiquitin-dependent proteolysis. Proc Natl Acad Sci U S A 2005; 102:15280-2; PMID:16230621; http://dx.doi.org/10.1073/pnas.0504842102
5. Lee I, Schindelin H. Structural insights into E1-catalyzed ubiquitin activation and transfer to conjugating enzymes. Cell 2008; 134:268-78; PMID:18662542; http://dx.doi.org/10.1016/j.cell.2008.05.046
6. van Wijk SJ, Timmers HT. The family of ubiquitin-conjugating enzymes (E2s): deciding between life and death of proteins. FASEB J 2010; 24:981-93; PMID:19940261; http://dx.doi.org/10.1096/fj.09-136259
7. Ardley HC, Robinson PA. E3 ubiquitin ligases. Essays Biochem 2005; 41:15-30; PMID:16250895; http://dx.doi.org/10.1042/EB0410015
8. Deshaies RJ, Joazeiro CA. RING domain E3 ubiquitin ligases. Annu Rev Biochem 2009; 78:399-434; PMID:19489725; http://dx.doi.org/10.1146/annurev.biochem.78.101807.093809
9. Thrower JS, Hoffman L, Rechsteiner M, Pickart CM. Recognition of the polyubiquitin proteolytic signal. EMBO J 2000; 19:94-102; PMID:10619848; http://dx.doi.org/10.1093/emboj/19.1.94
10. da Fonseca PC, He J, Morris EP. Molecular model of the human 26S proteasome. Mol Cell 2012; 46:54-66; PMID:22500737; http://dx.doi.org/10.1016/j.molcel.2012.03.026
11. Lasker K, Forster F, Bohn S, Walzthoeni T, Villa E, Unverdorben P, Beck F, Aebersold R, Sali A, Baumeister W. Molecular architecture of the 26S proteasome holocomplex determined by an integrative approach. Proc Natl Acad Sci U S A 2012; 109:1380-7; PMID:22307589; http://dx.doi.org/10.1073/pnas.1120559109
12. Lander GC, Estrin E, Matyskiela ME, Bashore C, Nogales E, Martin A. Complete subunit architecture of the proteasome regulatory particle. Nature 2012; 482:186-91; PMID:22237024; http://dx.doi.org/10.1038/nature10774
13. Adams J. The proteasome: structure, function, and role in the cell. Cancer Treat Rev 2003; 29 Suppl 1:3-9; PMID:12738238; http://dx.doi.org/10.1016/S0305-7372(03)00081-1
14. Coux O, Tanaka K, Goldberg AL. Structure and functions of the 20S and 26S proteasomes. Annu Rev Biochem 1996; 65:801-47; PMID:8811196; http://dx.doi.org/10.1146/annurev.bi.65.070196.004101
15. Glickman MH, Rubin DM, Coux O, Wefes I, Pfeifer G, Cjeka Z, Baumeister W, Fried VA, Finley D. A subcomplex of the proteasome regulatory particle required for ubiquitin-conjugate degradation and related to the COP9-signalosome and eIF3. Cell 1998; 94:615-23; PMID:9741626; http://dx.doi.org/10.1016/S0092-8674(00)81603-7
16. Koulich E, Li X, DeMartino GN. Relative structural and functional roles of multiple deubiquitylating proteins associated with mammalian 26S proteasome. Mol Biol Cell 2008; 19:1072-82; PMID:18162577; http://dx.doi.org/10.1091/mbc.E07-10-1040
17. Hanna J, Hathaway NA, Tone Y, Crosas B, Elsasser S, Kirkpatrick DS, Leggett DS, Gygi SP, King RW, Finley D. Deubiquitinating enzyme Ubp6 functions noncatalytically to delay proteasomal degradation. Cell 2006; 127:99-111; PMID:17018280; http://dx.doi.org/10.1016/j.cell.2006.07.038
18. Verma R, Aravind L, Oania R, McDonald WH, Yates JR, 3rd, Koonin EV, Deshaies RJ. Role of Rpn11 metalloprotease in deubiquitination and degradation by the 26S proteasome. Science 2002; 298:611-5; PMID:12183636; http://dx.doi.org/10.1126/science.1075898
19. Pickart CM, Cohen RE. Proteasomes and their kin: proteases in the machine age. Nat Rev Mol Cell Biol 2004; 5:177-87; PMID:14990998; http://dx.doi.org/10.1038/nrm1336
20. Unno M, Mizushima T, Morimoto Y, Tomisugi Y, Tanaka K, Yasuoka N, Tsukihara T. The structure of the mammalian 20S proteasome at 2.75 A resolution. Structure 2002; 10:609-18; PMID:12015144; http://dx.doi.org/10.1016/S0969-2126(02)00748-7
21. Lee C, Schwartz MP, Prakash S, Iwakura M, Matouschek A. ATP-dependent proteases degrade their substrates by processively unraveling them from the degradation signal. Mol Cell 2001; 7:627-37; PMID:11463387; http://dx.doi.org/10.1016/S1097-2765(01)00209-X
22. Groll M, Bajorek M, Kohler A, Moroder L, Rubin DM, Huber R, Glickman MH, Finley D. A gated channel into the proteasome core particle. Nat Struct Biol 2000; 7:1062-7; PMID:11062564; http://dx.doi.org/10.1038/80992
23. Kisselev AF, Akopian TN, Woo KM, Goldberg AL. The sizes of peptides generated from protein by mammalian 26 and 20 S proteasomes. Implications for understanding the degradative mechanism and antigen presentation. J Biol Chem 1999; 274:3363-71; PMID:9920878; http://dx.doi.org/10.1074/jbc.274.6.3363
24. Komander D, Rape M. The ubiquitin code. Annu Rev Biochem 2012; 81:203-29; PMID:22524316; http://dx.doi.org/10.1146/annurev-biochem-060310-170328
25. Husnjak K, Dikic I. Ubiquitin-binding proteins: decoders of ubiquitin-mediated cellular functions. Annu Rev Biochem 2012; 81:291-322; PMID:22482907; http://dx.doi.org/10.1146/annurev-biochem-051810-094654
26. Fraile JM, Quesada V, Rodriguez D, Freije JM, Lopez-Otin C. Deubiquitinases in cancer: new functions and therapeutic options. Oncogene 2012; 31:2373-88; PMID:21996736; http://dx.doi.org/10.1038/onc.2011.443
27. Bedford L, Lowe J, Dick LR, Mayer RJ, Brownell JE. Ubiquitin-like protein conjugation and the ubiquitin-proteasome system as drug targets. Nat Rev Drug Discov 2011; 10:29-46; PMID:21151032; http://dx.doi.org/10.1038/nrd3321
28. Xu P, Duong DM, Seyfried NT, Cheng D, Xie Y, Robert J, Rush J, Hochstrasser M, Finley D, Peng J. Quantitative proteomics reveals the function of unconventional ubiquitin chains in proteasomal degradation. Cell 2009; 137:133-45; PMID:19345192; http://dx.doi.org/10.1016/j.cell.2009.01.041
29. Tokunaga F, Nakagawa T, Nakahara M, Saeki Y, Taniguchi M, Sakata S, Tanaka K, Nakano H, Iwai K. SHARPIN is a component of the NF-kappaB-activating linear ubiquitin chain assembly complex. Nature 2011; 471:633-6; PMID:21455180; http://dx.doi.org/10.1038/nature09815
30. Tokunaga F, Sakata S, Saeki Y, Satomi Y, Kirisako T, Kamei K, Nakagawa T, Kato M, Murata S, Yamaoka S, et al. Involvement of linear polyubiquitylation of NEMO in NF-kappaB activation. Nat Cell Biol 2009; 11:123-32; PMID:19136968; http://dx.doi.org/10.1038/ncb1821
31. Clague MJ, Barsukov I, Coulson JM, Liu H, Rigden DJ, Urbe S. Deubiquitylases from genes to organism. Physiol Rev 2013; 93:1289-315; PMID:23899565; http://dx.doi.org/10.1152/physrev.00002.2013
32. Rieser E, Cordier SM, Walczak H. Linear ubiquitination: a newly discovered regulator of cell signalling. Trends Biochem Sci 2013; 38:94-102; PMID:23333406; http://dx.doi.org/10.1016/j.tibs.2012.11.007
33. Skaar JR, Pagano M. Control of cell growth by the SCF and APC/C ubiquitin ligases. Curr Opin Cell Biol 2009; 21:816-24; PMID:19775879; http://dx.doi.org/10.1016/j.ceb.2009.08.004
34. Ciechanover A, Stanhill A. The complexity of recognition of ubiquitinated substrates by the 26S proteasome. Biochim Biophys Acta 2014; 1843:86-96; PMID:23872423; http://dx.doi.org/10.1016/j.bbamcr.2013.07.007
35. Amm I, Sommer T, Wolf DH. Protein quality control and elimination of protein waste: the role of the ubiquitin-proteasome system. Biochim Biophys Acta 2014; 1843:182-96; PMID:23850760; http://dx.doi.org/10.1016/j.bbamcr.2013.06.031
36. Fredrickson EK, Gardner RG. Selective destruction of abnormal proteins by ubiquitin-mediated protein quality control degradation. Semin Cell Dev Biol 2012; 23:530-7; PMID:22245831; http://dx.doi.org/10.1016/j.semcdb.2011.12.006
37. Galluzzi L, Bravo-San Pedro JM, Kroemer G. Organelle-specific initiation of cell death. Nat Cell Biol 2014:16(8):728-36 IN PRESS; PMID:25082195; http://dx.doi.org/10.1038/ncb3005
38. Galluzzi L, Kepp O, Kroemer G. Mitochondria: master regulators of danger signalling. Nat Rev Mol Cell Biol 2012; 13:780-8; PMID:23175281; http://dx.doi.org/10.1038/nrm3479
39. Galluzzi L, Vitale I, Abrams JM, Alnemri ES, Baehrecke EH, Blagosklonny MV, Dawson TM, Dawson

VL, El-Deiry WS, Fulda S et al. Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012. Cell Death Differ 2012; 19:107-20; PMID:21760595; http://dx.doi.org/10.1038/cdd.2011.96
40. Clague MJ, Liu H, Urbe S. Governance of endocytic trafficking and signaling by reversible ubiquitylation. Dev Cell 2012; 23:457-67; PMID:22975321; http://dx.doi.org/10.1016/j.devcel.2012.08.011
41. MacGurn JA, Hsu PC, Emr SD. Ubiquitin and membrane protein turnover: from cradle to grave. Annu Rev Biochem 2012; 81:231-59; PMID:22404628; http://dx.doi.org/10.1146/annurev-biochem-060210-093619
42. Galluzzi L, Kepp O, Vander Heiden MG, Kroemer G. Metabolic targets for cancer therapy. Nat Rev Drug Discov 2013; 12:829-46; PMID:24113830; http://dx.doi.org/10.1038/nrd4145
43. Green DR, Galluzzi L, Kroemer G. Mitochondria and the autophagy-inflammation-cell death axis in organismal aging. Science 2011; 333:1109-12; PMID:21868666; http://dx.doi.org/10.1126/science.1201940
44. Vucic D, Dixit VM, Wertz IE. Ubiquitylation in apoptosis: a post-translational modification at the edge of life and death. Nat Rev Mol Cell Biol 2011; 12:439-52; PMID:21697901; http://dx.doi.org/10.1038/nrm3143
45. Jin L, Williamson A, Banerjee S, Philipp I, Rape M. Mechanism of ubiquitin-chain formation by the human anaphase-promoting complex. Cell 2008; 133:653-65; PMID:18485873; http://dx.doi.org/10.1016/j.cell.2008.04.012
46. Mukhopadhyay D, Riezman H. Proteasome-independent functions of ubiquitin in endocytosis and signaling. Science 2007; 315:201-5; PMID:17218518; http://dx.doi.org/10.1126/science.1127085
47. Hicke L, Dunn R. Regulation of membrane protein transport by ubiquitin and ubiquitin-binding proteins. Annu Rev Cell Dev Biol 2003; 19:141-72; PMID:14570567; http://dx.doi.org/10.1146/annurev.cellbio.19.110701.154617
48. Hicke L. Protein regulation by monoubiquitin. Nat Rev Mol Cell Biol 2001; 2:195-201; PMID:11265249; http://dx.doi.org/10.1038/35056583
49. Voutsadakis IA. Ubiquitination and the Ubiquitin-Proteasome System as regulators of transcription and transcription factors in epithelial mesenchymal transition of cancer. Tumour Biol 2012; 33:897-910; PMID:22399444; http://dx.doi.org/10.1007/s13277-012-0355-x
50. Ma Y, Galluzzi L, Zitvogel L, Kroemer G. Autophagy and cellular immune responses. Immunity 2013; 39:211-27; PMID:23973220; http://dx.doi.org/10.1016/j.immuni.2013.07.017
51. Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. Immunity 2013; 39:74-88; PMID:23890065; http://dx.doi.org/10.1016/j.immuni.2013.06.014
52. Galluzzi L, Kepp O, Trojel-Hansen C, Kroemer G. Mitochondrial control of cellular life, stress, and death. Circ Res 2012; 111:1198-207; PMID:23065343; http://dx.doi.org/10.1161/CIRC-RESAHA.112.268946
53. Morselli E, Galluzzi L, Kepp O, Marino G, Michaud M, Vitale I, Maiuri MC, Kroemer G. Oncosuppressive functions of autophagy. Antioxid Redox Signal 2011; 14:2251-69; PMID:20712403; http://dx.doi.org/10.1089/ars.2010.3478
54. Morselli E, Galluzzi L, Kepp O, Vicencio JM, Criollo A, Maiuri MC, Kroemer G. Anti- and pro-tumor functions of autophagy. Biochim Biophys Acta 2009; 1793:1524-32; PMID:19371598; http://dx.doi.org/10.1016/j.bbamcr.2009.01.006
55. Garg AD, Dudek AM, Agostinis P. Autophagy-dependent suppression of cancer immunogenicity and effector mechanisms of innate and adaptive immunity. Oncoimmunology 2013; 2:e26260; PMID:24353910; http://dx.doi.org/10.4161/onci.26260
56. Yi Y, Zhou Z, Shu S, Fang Y, Twitty C, Hilton TL, Aung S, Urba WJ, Fox BA, Hu HM, et al. Autophagy-assisted antigen cross-presentation: autophagosome as the argo of shared tumor-specific antigens and DAMPs. Oncoimmunology 2012; 1:976-8; PMID:23162777; http://dx.doi.org/10.4161/onci.20059
57. Fujii S, Hara H, Araya J, Takasaka N, Kojima J, Ito S, Minagawa S, Yumino Y, Ishikawa T, Numata T, et al. Insufficient autophagy promotes bronchial epithelial cell senescence in chronic obstructive pulmonary disease. Oncoimmunology 2012; 1:630-41; PMID:22934255; http://dx.doi.org/10.4161/onci.20297
58. Ying Z, Wang H, Wang G. The ubiquitin proteasome system as a potential target for the treatment of neurodegenerative diseases. Curr Pharm Des 2013; 19:3305-14; PMID:23151138; http://dx.doi.org/10.2174/1381612811319180013
59. Rahimi N. The ubiquitin-proteasome system meets angiogenesis. Mol Cancer Ther 2012; 11:538-48; PMID:22357635; http://dx.doi.org/10.1158/1535-7163.MCT-11-0555
60. Dahlmann B. Role of proteasomes in disease. BMC Biochem 2007; 8 Suppl 1:S3; PMID:18047740; http://dx.doi.org/10.1186/1471-2091-8-S1-S3
61. Reinstein E, Ciechanover A. Narrative review: protein degradation and human diseases: the ubiquitin connection. Ann Intern Med 2006; 145:676-84; PMID:17088581; http://dx.doi.org/10.7326/0003-4819-145-9-200611070-00010
62. Herrmann J, Ciechanover A, Lerman LO, Lerman A. The ubiquitin-proteasome system in cardiovascular diseases-a hypothesis extended. Cardiovasc Res 2004; 61:11-21; PMID:14732197; http://dx.doi.org/10.1016/j.cardiores.2003.09.033
63. Adams J. The proteasome: a suitable antineoplastic target. Nat Rev Cancer 2004; 4:349-60; PMID:15122206; http://dx.doi.org/10.1038/nrc1361
64. Micel LN, Tentler JJ, Smith PG, Eckhardt GS. Role of ubiquitin ligases and the proteasome in oncogenesis: novel targets for anticancer therapies. J Clin Oncol 2013; 31:1231-8; PMID:23358974; http://dx.doi.org/10.1200/JCO.2012.44.0958
65. Bianchi G, Oliva L, Cascio P, Pengo N, Fontana F, Cerruti F, Orsi A, Pasqualetto E, Mezghrani A, Calbi V, et al. The proteasome load versus capacity balance determines apoptotic sensitivity of multiple myeloma cells to proteasome inhibition. Blood 2009; 113:3040-9; PMID:19164601; http://dx.doi.org/10.1182/blood-2008-08-172734
66. Nalepa G, Rolfe M, Harper JW. Drug discovery in the ubiquitin-proteasome system. Nat Rev Drug Discov 2006; 5:596-613; PMID:16816840; http://dx.doi.org/10.1038/nrd2056
67. Dobbelstein M, Moll U. Targeting tumour-supportive cellular machineries in anticancer drug development. Nat Rev Drug Discov 2014; 13:179-96; PMID:24577400; http://dx.doi.org/10.1038/nrd4201
68. Hoeller D, Dikic I. Targeting the ubiquitin system in cancer therapy. Nature 2009; 458:438-44; PMID:19325623; http://dx.doi.org/10.1038/nature07960
69. Chen L, Madura K. Increased proteasome activity, ubiquitin-conjugating enzymes, and eEF1A translation factor detected in breast cancer tissue. Cancer Res 2005; 65:5599-606; PMID:15994932; http://dx.doi.org/10.1158/0008-5472.CAN-05-0201
70. Luo J, Solimini NL, Elledge SJ. Principles of cancer therapy: oncogene and non-oncogene addiction. Cell 2009; 136:823-37; PMID:19269363; http://dx.doi.org/10.1016/j.cell.2009.02.024
71. Solimini NL, Luo J, Elledge SJ. Non-oncogene addiction and the stress phenotype of cancer cells. Cell 2007; 130:986-8; PMID:17889643; http://dx.doi.org/10.1016/j.cell.2007.09.007
72. Zhou YJ, Binder RJ. The heat shock protein-CD91 pathway mediates tumor immunosurveillance. Oncoimmunology 2014; 3:e28222; PMID:25050192; http://dx.doi.org/10.4161/onci.28222
73. Rao A, Lowe DB, Storkus WJ. Shock block for improved immunotherapy. Oncoimmunology 2012; 1:1427-9; PMID:23243617; http://dx.doi.org/10.4161/onci.21174
74. Yang Y, Lizee G, Hwu P. Strong emerging rationale for combining oncogene-targeted agents with immunotherapy. Oncoimmunology 2013; 2:e22730; PMID:23524978; http://dx.doi.org/10.4161/onci.22730
75. Poggi A, Zocchi MR. How to exploit stress-related immunity against Hodgkin's lymphoma: targeting ERp5 and ADAM sheddases. Oncoimmunology 2013; 2:e27089; PMID:24498565; http://dx.doi.org/10.4161/onci.27089
76. Demaria S, Pilones KA, Formenti SC, Dustin ML. Exploiting the stress response to radiation to sensitize poorly immunogenic tumors to anti-CTLA-4 treatment. Oncoimmunology 2013; 2:e23127; PMID:23802063; http://dx.doi.org/10.4161/onci.23127
77. Garg AD, Krysko DV, Vandenabeele P, Agostinis P. The emergence of phox-ER stress induced immunogenic apoptosis. Oncoimmunology 2012; 1:786-8; PMID:22934283; http://dx.doi.org/10.4161/onci.19750
78. Jagannath S, Barlogie B, Berenson J, Siegel D, Irwin D, Richardson PG, Niesvizky R, Alexanian R, Limentani SA, Alsina M, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol 2004; 127:165-72; PMID:15461622; http://dx.doi.org/10.1111/j.1365-2141.2004.05188.x
79. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, Rajkumar SV, Srkalovic G, Alsina M, Alexanian R, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003; 348:2609-17; PMID:12826635; http://dx.doi.org/10.1056/NEJMoa030288
80. Moreau P, Richardson PG, Cavo M, Orlowski RZ, San Miguel JF, Palumbo A, Harousseau JL. Proteasome inhibitors in multiple myeloma: 10 years later. Blood 2012; 120:947-59; PMID:22645181; http://dx.doi.org/10.1182/blood-2012-04-403733
81. Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC. Multiple myeloma. Lancet 2009; 374:324-39; PMID:19541364; http://dx.doi.org/10.1016/S0140-6736(09)60221-X
82. Chen P, Balachandran S. Development of interferon gamma-based immunocytokines targeting renal cancer. Oncoimmunology 2013; 2:e24964; PMID:24073376; http://dx.doi.org/10.4161/onci.24964
83. Goy A, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, de Vos S, Epner E, Krishnan A, Leonard JP, Lonial S, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Oncol 2009; 20:520-5; PMID:19074748; http://dx.doi.org/10.1093/annonc/mdn656
84. Fisher RI, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, de Vos S, Epner E, Krishnan A, Leonard JP, Lonial S, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2006; 24:4867-74; PMID:17001068; http://dx.doi.org/10.1200/JCO.2006.07.9665
85. Jagannath S, Vij R, Stewart AK, Trudel S, Jakubowiak AJ, Reiman T, Somlo G, Bahlis N, Lonial S, Kunkel LA, et al. An open-label single-arm pilot phase II study (PX-171-003-A0) of low-dose, single-agent carfilzomib in patients with relapsed and refractory multiple myeloma. Clin Lymphoma Myeloma Leuk 2012; 12:310-8; PMID:23040437; http://dx.doi.org/10.1016/j.clml.2012.08.003

86. Vij R, Siegel DS, Jagannath S, Jakubowiak AJ, Stewart AK, McDonagh K, Bahlis N, Belch A, Kunkel LA, Wear S et al. An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib. Br J Haematol 2012; 158:739-48; PMID:22845873; http://dx.doi.org/10.1111/j.1365-2141.2012.09232.x
87. Siegel DS, Martin T, Wang M, Vij R, Jakubowiak AJ, Lonial S, Trudel S, Kukreti V, Bahlis N, Alsina M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood 2012; 120:2817-25; PMID:22833546; http://dx.doi.org/10.1182/blood-2012-05-425934
88. Vij R, Wang M, Kaufman JL, Lonial S, Jakubowiak AJ, Stewart AK, Kukreti V, Jagannath S, McDonagh KT, Alsina M, et al. An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. Blood 2012; 119:5661-70; PMID:22555973; http://dx.doi.org/10.1182/blood-2012-03-414359
89. Etlinger JD, Goldberg AL. A soluble ATP-dependent proteolytic system responsible for the degradation of abnormal proteins in reticulocytes. Proc Natl Acad Sci U S A 1977; 74:54-8; PMID:264694; http://dx.doi.org/10.1073/pnas.74.1.54
90. Glickman MH, Ciechanover A. The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction. Physiol Rev 2002; 82:373-428; PMID:11917093
91. Hershko A, Ciechanover A. The ubiquitin system. Annu Rev Biochem 1998; 67:425-79; PMID:9759494; http://dx.doi.org/10.1146/annurev.biochem.67.1.425
92. Ciehanover A, Hod Y, Hershko A. A heat-stable polypeptide component of an ATP-dependent proteolytic system from reticulocytes. Biochem Biophys Res Commun 1978; 81:1100-5; PMID:666810; http://dx.doi.org/10.1016/0006-291X(78)91249-4
93. Wilkinson KD. Ubiquitin: a Nobel protein. Cell 2004; 119:741-5; PMID:15607971
94. Hough R, Pratt G, Rechsteiner M. Purification of two high molecular weight proteases from rabbit reticulocyte lysate. J Biol Chem 1987; 262:8303-13; PMID:3298229
95. Schmid HP, Akhayat O, Martins De Sa C, Puvion F, Koehler K, Scherrer K. The prosome: an ubiquitous morphologically distinct RNP particle associated with repressed mRNPs and containing specific ScRNA and a characteristic set of proteins. EMBO J 1984; 3:29-34; PMID:6200323
96. Wilk S, Orlowski M. Evidence that pituitary cation-sensitive neutral endopeptidase is a multicatalytic protease complex. J Neurochem 1983; 40:842-9; PMID:6338156; http://dx.doi.org/10.1111/j.1471-4159.1983.tb08056.x
97. Jagannath S, Barlogie B, Berenson JR, Siegel DS, Irwin D, Richardson PG, Niesvizky R, Alexanian R, Limentani SA, Alsina M, et al. Updated survival analyses after prolonged follow-up of the phase 2, multicenter CREST study of bortezomib in relapsed or refractory multiple myeloma. Br J Haematol 2008; 143:537-40; PMID:18783399; http://dx.doi.org/10.1111/j.1365-2141.2008.07359.x
98. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005; 352:2487-98; PMID:15958804; http://dx.doi.org/10.1056/NEJMoa043445
99. Adams J. Development of the proteasome inhibitor PS-341. Oncologist 2002; 7:9-16; PMID:11854543; http://dx.doi.org/10.1634/theoncologist.7-1-9
100. Adams J, Palombella VJ, Sausville EA, Johnson J, Destree A, Lazarus DD, Maas J, Pien CS, Prakash S, Elliott PJ. Proteasome inhibitors: a novel class of potent and effective antitumor agents. Cancer Res 1999; 59:2615-22; PMID:10363983
101. Aranda F, Vacchelli E, Eggermont A, Galon J, Fridman WH, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: immunostimulatory monoclonal antibodies in cancer therapy. Oncoimmunology 2014; 3:e27297; PMID:24701370; http://dx.doi.org/10.4161/onci.27297
102. Aranda F, Vacchelli E, Eggermont A, Galon J, Sautes-Fridman C, Tartour E, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: peptide vaccines in cancer therapy. Oncoimmunology 2013; 2:e26621; PMID:24498550; http://dx.doi.org/10.4161/onci.26621
103. Vacchelli E, Aranda F, Eggermont A, Galon J, Sautes-Fridman C, Cremer I, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: chemotherapy with immunogenic cell death inducers. Oncoimmunology 2014; 3:e27878; PMID:24800173; http://dx.doi.org/10.4161/onci.27878
104. Vacchelli E, Aranda F, Eggermont A, Galon J, Sautes-Fridman C, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: tumor-targeting monoclonal antibodies in cancer therapy. Oncoimmunology 2014; 3:e27048; PMID:24605265; http://dx.doi.org/10.4161/onci.27048
105. Galluzzi L, Vacchelli E, Eggermont A, Fridman WH, Galon J, Sautes-Fridman C, Tartour E, Zitvogel L, Kroemer G. Trial Watch: experimental toll-like receptor agonists for cancer therapy. Oncoimmunology 2012; 1:699-716; PMID:22934262; http://dx.doi.org/10.4161/onci.20696
106. Galluzzi L, Vacchelli E, Fridman WH, Galon J, Sautes-Fridman C, Tartour E, Zucman-Rossi J, Zitvogel L, Kroemer G. Trial Watch: monoclonal antibodies in cancer therapy. Oncoimmunology 2012; 1:28-37; PMID:22720209; http://dx.doi.org/10.4161/onci.1.1.17938
107. Kronke J, Udeshi ND, Narla A, Grauman P, Hurst SN, McConkey M, Svinkina T, Heckl D, Comer E, Li X, et al. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. Science 2014; 343:301-5; PMID:24292625; http://dx.doi.org/10.1126/science.1244851
108. Lu G, Middleton RE, Sun H, Naniong M, Ott CJ, Mitsiades CS, Wong KK, Bradner JE, Kaelin WG Jr. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. Science 2014; 343:305-9; PMID:24292623; http://dx.doi.org/10.1126/science.1244917
109. Semeraro M, Galluzzi L. Novel insights into the mechanism of action of lenalidomide. Oncoimmunology 2014; 3:e28386; PMID:25340011; http://dx.doi.org/10.4161/onci.28386
110. Semeraro M, Vacchelli E, Eggermont A, Galon J, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: lenalidomide-based immunochemotherapy. Oncoimmunology 2013; 2:e26494; PMID:24482747; http://dx.doi.org/10.4161/onci.26494
111. Nikseresht M, Seghatoleslam A, Monabati A, Talei A, Ghalati FB, Owji AA. Overexpression of the novel human gene, UBE2Q2, in breast cancer. Cancer Genet Cytogenet 2010; 197:101-6; PMID:20193842; http://dx.doi.org/10.1016/j.cancergencyto.2009.11.020
112. Maeda H, Miyajima N, Kano S, Tsukiyama T, Okumura F, Fukuda S, Hatakeyama S. Ubiquitin-conjugating enzyme UBE2Q2 suppresses cell proliferation and is down-regulated in recurrent head and neck cancer. Mol Cancer Res 2009; 7:1553-62; PMID:19723876; http://dx.doi.org/10.1158/1541-7786.MCR-08-0543
113. Hao J, Xu A, Xie X, Hao J, Tian T, Gao S, Xiao X, He D. Elevated expression of UBE2T in lung cancer tumors and cell lines. Tumour Biol 2008; 29:195-203; PMID:18667844; http://dx.doi.org/10.1159/000148187
114. Sanders MA, Brahemi G, Nangia-Makker P, Balan V, Morelli M, Kothayer H, Westwell AD, Shekhar MP. Novel inhibitors of Rad6 ubiquitin conjugating enzyme: design, synthesis, identification, and functional characterization. Mol Cancer Ther 2013; 12:373-83; PMID:23339190; http://dx.doi.org/10.1158/1535-7163.MCT-12-0793
115. Shekhar MP, Lyakhovich A, Visscher DW, Heng H, Kondrat N. Rad6 overexpression induces multinucleation, centrosome amplification, abnormal mitosis, aneuploidy, and transformation. Cancer Res 2002; 62:2115-24; PMID:11929833
116. Summers MK, Pan B, Mukhyala K, Jackson PK. The unique N terminus of the UbcH10 E2 enzyme controls the threshold for APC activation and enhances checkpoint regulation of the APC. Mol Cell 2008; 31:544-56; PMID:18722180; http://dx.doi.org/10.1016/j.molcel.2008.07.014
117. Jiang L, Huang CG, Lu YC, Luo C, Hu GH, Liu HM, Chen JX, Han HX. Expression of ubiquitin-conjugating enzyme E2C/UbcH10 in astrocytic tumors. Brain Res 2008; 1201:161-6; PMID:18331723; http://dx.doi.org/10.1016/j.brainres.2008.01.037
118. Berlingieri MT, Pallante P, Guida M, Nappi C, Masciullo V, Scambia G, Ferraro A, Leone V, Sboner A, Barbareschi M, et al. UbcH10 expression may be a useful tool in the prognosis of ovarian carcinomas. Oncogene 2007; 26:2136-40; PMID:17016443; http://dx.doi.org/10.1038/sj.onc.1210010
119. Wagner KW, Sapinoso LM, El-Rifai W, Frierson HF, Butz N, Mestan J, Hofmann F, Deveraux QL, Hampton GM. Overexpression, genomic amplification and therapeutic potential of inhibiting the UbcH10 ubiquitin conjugase in human carcinomas of diverse anatomic origin. Oncogene 2004; 23:6621-9; PMID:15208666; http://dx.doi.org/10.1038/sj.onc.1207861
120. van Ree JH, Jeganathan KB, Malureanu L, van Deursen JM. Overexpression of the E2 ubiquitin-conjugating enzyme UbcH10 causes chromosome missegregation and tumor formation. J Cell Biol 2010; 188:83-100; PMID:20065091; http://dx.doi.org/10.1083/jcb.200906147
121. Vitale I, Galluzzi L, Castedo M, Kroemer G. Mitotic catastrophe: a mechanism for avoiding genomic instability. Nat Rev Mol Cell Biol 2011; 12:385-92; PMID:21527953; http://dx.doi.org/10.1038/nrm3115
122. Vitale I, Galluzzi L, Senovilla L, Criollo A, Jemaa M, Castedo M, Kroemer G. Illicit survival of cancer cells during polyploidization and depolyploidization. Cell Death Differ 2011; 18:1403-13; PMID:21072053; http://dx.doi.org/10.1038/cdd.2010.145
123. Senovilla L, Vitale I, Martins I, Kepp O, Galluzzi L, Zitvogel L, Castedo M, Kroemer G. An anticancer therapy-elicited immunosurveillance system that eliminates tetraploid cells. Oncoimmunology 2013; 2:e22409; PMID:23482968; http://dx.doi.org/10.4161/onci.22409
124. Galluzzi L, Morselli E, Kepp O, Vitale I, Pinti M, Kroemer G. Mitochondrial liaisons of p53. Antioxid Redox Signal 2011; 15:1691-714; PMID:20712408; http://dx.doi.org/10.1089/ars.2010.3504
125. Eymin B, Gazzeri S, Brambilla C, Brambilla E. Mdm2 overexpression and p14(ARF) inactivation are two mutually exclusive events in primary human lung tumors. Oncogene 2002; 21:2750-61; PMID:11965548; http://dx.doi.org/10.1038/sj.onc.1205359
126. Polsky D, Bastian BC, Hazan C, Melzer K, Pack J, Houghton A, Busam K, Cordon-Cardo C, Osman I. HDM2 protein overexpression, but not gene amplification, is related to tumorigenesis of cutaneous melanoma. Cancer Res 2001; 61:7642-6; PMID:11606406
127. Momand J, Jung D, Wilczynski S, Niland J. The MDM2 gene amplification database. Nucleic Acids

Res 1998; 26:3453-9; PMID:9671804; http://dx.doi.org/10.1093/nar/26.15.3453
128. Reifenberger G, Liu L, Ichimura K, Schmidt EE, Collins VP. Amplification and overexpression of the MDM2 gene in a subset of human malignant gliomas without p53 mutations. Cancer Res 1993; 53:2736-9; PMID:8504413
129. Zirngibl K, Moll UM. p53 further extends its reach. Oncoimmunology 2013; 2:e24959; PMID:24255806; http://dx.doi.org/10.4161/onci.24959
130. Mandapathil M, Visus C, Finn OJ, Lang S, Whiteside TL. Generation and immunosuppressive functions of p53-induced human adaptive regulatory T cells. Oncoimmunology 2013; 2:e25514; PMID:24073385; http://dx.doi.org/10.4161/onci.25514
131. Li H, Lakshmikanth T, Carbone E, Selivanova G. A novel facet of tumor suppression by p53: induction of tumor immunogenicity. Oncoimmunology 2012; 1:541-3; PMID:22754780; http://dx.doi.org/10.4161/onci.19409
132. Chen D, Brooks CL, Gu W. ARF-BP1 as a potential therapeutic target. Br J Cancer 2006; 94:1555-8; PMID:16641901
133. Adhikary S, Marinoni F, Hock A, Hulleman E, Popov N, Beier R, Bernard S, Quarto M, Capra M, Goettig S, et al. The ubiquitin ligase HectH9 regulates transcriptional activation by Myc and is essential for tumor cell proliferation. Cell 2005; 123:409-21; PMID:16269333; http://dx.doi.org/10.1016/j.cell.2005.08.016
134. Chen D, Kon N, Li M, Zhang W, Qin J, Gu W. ARF-BP1/Mule is a critical mediator of the ARF tumor suppressor. Cell 2005; 121:1071-83; PMID:15989956; http://dx.doi.org/10.1016/j.cell.2005.03.037
135. Pello OM, Andres V. Role of c-MYC in tumor-associated macrophages and cancer progression. Oncoimmunology 2013; 2:e22984; PMID:23526468; http://dx.doi.org/10.4161/onci.22984
136. Zhou Z, Liu R, Chen C. The WWP1 ubiquitin E3 ligase increases TRAIL resistance in breast cancer. Int J Cancer 2012; 130:1504-10; PMID:21480222; http://dx.doi.org/10.1002/ijc.26122
137. Zhi X, Zhao D, Wang Z, Zhou Z, Wang C, Chen W, Liu R, Chen C. E3 ubiquitin ligase RNF126 promotes cancer cell proliferation by targeting the tumor suppressor p21 for ubiquitin-mediated degradation. Cancer Res 2013; 73:385-94; PMID:23026136; http://dx.doi.org/10.1158/0008-5472.CAN-12-0562
138. Fukuchi M, Masuda N, Nakajima M, Fukai Y, Miyazaki T, Kato H, Kuwano H. Inverse correlation between expression levels of p27 and the ubiquitin ligase subunit Skp2 in early esophageal squamous cell carcinoma. Anticancer Res 2004; 24:777-83; PMID:15161026
139. Ben-Izhak O, Lahav-Baratz S, Meretyk S, Ben-Eliezer S, Sabo E, Dirnfeld M, Cohen S, Ciechanover A. Inverse relationship between Skp2 ubiquitin ligase and the cyclin dependent kinase inhibitor p27Kip1 in prostate cancer. J Urol 2003; 170:241-5; PMID:12796697; http://dx.doi.org/10.1097/01.ju.0000072113.34524.a7
140. Masuda TA, Inoue H, Sonoda H, Mine S, Yoshikawa Y, Nakayama K, Mori M. Clinical and biological significance of S-phase kinase-associated protein 2 (Skp2) gene expression in gastric carcinoma: modulation of malignant phenotype by Skp2 overexpression, possibly via p27 proteolysis. Cancer Res 2002; 62:3819-25; PMID:12097295
141. Chiarle R, Fan Y, Piva R, Boggino H, Skolnik J, Novero D, Palestro G, De Wolf-Peeters C, Chilosi M, Pagano M, et al. S-phase kinase-associated protein 2 expression in non-Hodgkin's lymphoma inversely correlates with p27 expression and defines cells in S phase. Am J Pathol 2002; 160:1457-66; PMID:11943729; http://dx.doi.org/10.1016/S0002-9440(10)62571-0
142. Hershko D, Bornstein G, Ben-Izhak O, Carrano A, Pagano M, Krausz MM, Hershko A. Inverse relation between levels of p27(Kip1) and of its ubiquitin ligase subunit Skp2 in colorectal carcinomas. Cancer 2001; 91:1745-51; PMID:11335900; http://dx.doi.org/10.1002/1097-0142(20010501)91:9%3c1745::AID-CNCR1193%3e3.0.CO;2-H
143. Carrano AC, Eytan E, Hershko A, Pagano M. SKP2 is required for ubiquitin-mediated degradation of the CDK inhibitor p27. Nat Cell Biol 1999; 1:193-9; PMID:10559916; http://dx.doi.org/10.1038/12013
144. Hsieh SC, Kuo SN, Zheng YH, Tsai MH, Lin YS, Lin JH. The E3 ubiquitin ligase SIAH2 is a prosurvival factor overexpressed in oral cancer. Anticancer Res 2013; 33:4965-73; PMID:24222137
145. Burger AM, Gao Y, Amemiya Y, Kahn HJ, Kitching R, Yang Y, Sun P, Narod SA, Hanna WM, Seth AK. A novel RING-type ubiquitin ligase breast cancer-associated gene 2 correlates with outcome in invasive breast cancer. Cancer Res 2005; 65:10401-12; PMID:16288031; http://dx.doi.org/10.1158/0008-5472.CAN-05-2103
146. King EV, Ottensmeier CH, Thomas GJ. The immune response in HPV oropharyngeal cancer. Oncoimmunology 2014; 3:e27254; PMID:24575385; http://dx.doi.org/10.4161/onci.27254
147. Nizard M, Sandoval F, Badoual C, Pere H, Terme M, Hans S, Benhamouda N, Granier C, Brasnu D, Tartour E. Immunotherapy of HPV-associated head and neck cancer: critical parameters. Oncoimmunology 2013; 2:e24534; PMID:23894716; http://dx.doi.org/10.4161/onci.24534
148. Lehtinen M, Paavonen J. Sound efficacy of prophylactic HPV vaccination: basics and implications. Oncoimmunology 2012; 1:995-6; PMID:23162784; http://dx.doi.org/10.4161/onci.20011
149. Scheffner M, Takahashi T, Huibregtse JM, Minna JD, Howley PM. Interaction of the human papillomavirus type 16 E6 oncoprotein with wild-type and mutant human p53 proteins. J Virol 1992; 66:5100-5; PMID:1321290
150. Scheffner M, Werness BA, Huibregtse JM, Levine AJ, Howley PM. The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. Cell 1990; 63:1129-36; PMID:2175676; http://dx.doi.org/10.1016/0092-8674(90)90409-8
151. Werness BA, Levine AJ, Howley PM. Association of human papillomavirus types 16 and 18 E6 proteins with p53. Science 1990; 248:76-9; PMID:2157286; http://dx.doi.org/10.1126/science.2157286
152. Barbieri CE, Baca SC, Lawrence MS, Demichelis F, Blattner M, Theurillat JP, White TA, Stojanov P, Van Allen E, Stransky N, et al. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. Nat Genet 2012; 44:685-9; PMID:22610119; http://dx.doi.org/10.1038/ng.2279
153. Elia AE, Elledge SJ. BRCA1 as tumor suppressor: lord without its RING? Breast Cancer Res 2012; 14:306; PMID:22494569; http://dx.doi.org/10.1186/bcr3118
154. Drost R, Bouwman P, Rottenberg S, Boon U, Schut E, Klarenbeek S, Klijn C, van der Heijden I, van der Gulden H, Wientjens E, et al. BRCA1 RING function is essential for tumor suppression but dispensable for therapy resistance. Cancer Cell 2011; 20:797-809; PMID:22172724; http://dx.doi.org/10.1016/j.ccr.2011.11.014
155. Shakya R, Reid LJ, Reczek CR, Cole F, Egli D, Lin CS, deRooij DG, Hirsch S, Ravi K, Hicks JB, et al. BRCA1 tumor suppression depends on BRCT phosphoprotein binding, but not its E3 ligase activity. Science 2011; 334:525-8; PMID:22034435; http://dx.doi.org/10.1126/science.1209909
156. Ruffner H, Joazeiro CA, Hemmati D, Hunter T, Verma IM. Cancer-predisposing mutations within the RING domain of BRCA1: loss of ubiquitin protein ligase activity and protection from radiation hypersensitivity. Proc Natl Acad Sci U S A 2001; 98:5134-9; PMID:11320250; http://dx.doi.org/10.1073/pnas.081068398
157. Kaelin WG. Von Hippel-Lindau disease. Annu Rev Pathol 2007; 2:145-73; PMID:18039096; http://dx.doi.org/10.1146/annurev.pathol.2.010506.092049
158. Inuzuka H, Shaik S, Onoyama I, Gao D, Tseng A, Maser RS, Zhai B, Wan L, Gutierrez A, Lau AW, et al. SCF(FBW7) regulates cellular apoptosis by targeting MCL1 for ubiquitylation and destruction. Nature 2011; 471:104-9; PMID:21368833; http://dx.doi.org/10.1038/nature09732
159. Welcker M, Clurman BE. FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation. Nat Rev Cancer 2008; 8:83-93; PMID:18094723; http://dx.doi.org/10.1038/nrc2290
160. Wang Z, Inuzuka H, Zhong J, Wan L, Fukushima H, Sarkar FH, Wei W. Tumor suppressor functions of FBW7 in cancer development and progression. FEBS Lett 2012; 586:1409-18; PMID:22673505; http://dx.doi.org/10.1016/j.febslet.2012.03.017
161. Cheng Y, Li G. Role of the ubiquitin ligase Fbw7 in cancer progression. Cancer Metastasis Rev 2012; 31:75-87; PMID:22124735; http://dx.doi.org/10.1007/s10555-011-9330-z
162. Nijhawan D, Zack TI, Ren Y, Strickland MR, Lamothe R, Schumacher SE, Tsherniak A, Besche HC, Rosenbluh J, Shehata S, et al. Cancer vulnerabilities unveiled by genomic loss. Cell 2012; 150:842-54; PMID:22901813; http://dx.doi.org/10.1016/j.cell.2012.07.023
163. Hayashi M, Jono H, Shinriki S, Nakamura T, Guo J, Sueta A, Tomiguchi M, Fujiwara S, Yamamoto-Ibusuki M, Murakami K, et al. Clinical significance of CYLD downregulation in breast cancer. Breast Cancer Res Treat 2014; 143:447-57; PMID:24398777; http://dx.doi.org/10.1007/s10549-013-2824-3
164. Galluzzi L, Kepp O, Krautwald S, Kroemer G, Linkermann A. Molecular mechanisms of regulated necrosis. Semin Cell Dev Biol 2014; PMID:24582829; http://dx.doi.org/10.1016/j.semcdb.2014.02.006
165. Vandenabeele P, Galluzzi L, Vanden Berghe T, Kroemer G. Molecular mechanisms of necroptosis: an ordered cellular explosion. Nat Rev Mol Cell Biol 2010; 11:700-14; PMID:20823910; http://dx.doi.org/10.1038/nrm2970
166. Galluzzi L, Kroemer G. Necroptosis: a specialized pathway of programmed necrosis. Cell 2008; 135:1161-3; PMID:19109884; http://dx.doi.org/10.1016/j.cell.2008.12.004
167. Guerriero JL, Ditsworth D, Zong WX. Non-apoptotic routes to defeat cancer. Oncoimmunology 2012; 1:94-6; PMID:22720222; http://dx.doi.org/10.4161/onci.1.1.17885
168. Williams SA, Maecker HL, French DM, Liu J, Gregg A, Silverstein LB, Cao TC, Carano RA, Dixit VM. USP1 deubiquitinates ID proteins to preserve a mesenchymal stem cell program in osteosarcoma. Cell 2011; 146:918-30; PMID:21925315; http://dx.doi.org/10.1016/j.cell.2011.07.040
169. Shan J, Zhao W, Gu W. Suppression of cancer cell growth by promoting cyclin D1 degradation. Mol Cell 2009; 36:469-76; PMID:19917254; http://dx.doi.org/10.1016/j.molcel.2009.10.018
170. Stevenson LF, Sparks A, Allende-Vega N, Xirodimas DP, Lane DP, Saville MK. The deubiquitinating enzyme USP2a regulates the p53 pathway by targeting Mdm2. EMBO J 2007; 26:976-86; PMID:17290220; http://dx.doi.org/10.1038/sj.emboj.7601567
171. Benassi B, Flavin R, Marchionni L, Zanata S, Pan Y, Chowdhury D, Marani M, Strano S, Muti P, Blandino G, et al. MYC is activated by USP2a-mediated modulation of microRNAs in prostate cancer. Cancer Discov 2012; 2:236-47; PMID:22585994; http://dx.doi.org/10.1158/2159-8290.CD-11-0219
172. Priolo C, Tang D, Brahamandan M, Benassi B, Sicinska E, Ogino S, Farsetti A, Porrello A, Finn S, Zimmermann J, et al. The isopeptidase USP2a protects

human prostate cancer from apoptosis. Cancer Res 2006; 66:8625-32; PMID:16951176; http://dx.doi.org/10.1158/0008-5472.CAN-06-1374
173. Schwickart M, Huang X, Lill JR, Liu J, Ferrando R, French DM, Maecker H, O'Rourke K, Bazan F, Eastham-Anderson J, et al. Deubiquitinase USP9X stabilizes MCL1 and promotes tumour cell survival. Nature 2010; 463:103-7; PMID:20023629; http://dx.doi.org/10.1038/nature08646
174. Kepp O, Galluzzi L, Lipinski M, Yuan J, Kroemer G. Cell death assays for drug discovery. Nat Rev Drug Discov 2011; 10:221-37; PMID:21358741; http://dx.doi.org/10.1038/nrd3373
175. Diefenbacher ME, Popov N, Blake SM, Schulein-Volk C, Nye E, Spencer-Dene B, Jaenicke LA, Eilers M, Behrens A. The deubiquitinase USP28 controls intestinal homeostasis and promotes colorectal cancer. J Clin Invest 2014; PMID:24960159; http://dx.doi.org/10.1172/JCI73733
176. Vazquez A, Bond EE, Levine AJ, Bond GL. The genetics of the p53 pathway, apoptosis and cancer therapy. Nat Rev Drug Discov 2008; 7:979-87; PMID:19043449; http://dx.doi.org/10.1038/nrd2656
177. Klein G. Tumor resistance. Oncoimmunology 2012; 1:1355-9; PMID:23243598; http://dx.doi.org/10.4161/onci.22194
178. Petroski MD. The ubiquitin system, disease, and drug discovery. BMC Biochem 2008; 9 Suppl 1:S7; PMID:19007437; http://dx.doi.org/10.1186/1471-2091-9-S1-S7
179. Orlowski RZ, Eswara JR, Lafond-Walker A, Grever MR, Orlowski M, Dang CV. Tumor growth inhibition induced in a murine model of human Burkitt's lymphoma by a proteasome inhibitor. Cancer Res 1998; 58:4342-8; PMID:9766662
180. Oromendia AB, Dodgson SE, Amon A. Aneuploidy causes proteotoxic stress in yeast. Genes Dev 2012; 26:2696-708; PMID:23222101; http://dx.doi.org/10.1101/gad.207407.112
181. Lim SY, Gordon-Weeks AN, Zhao L, Tapmeier TT, Im JH, Cao Y, Beech J, Allen D, Smart S, Muschel RJ, et al. Recruitment of myeloid cells to the tumor microenvironment supports liver metastasis. Oncoimmunology 2013; 2:e23187; PMID:23802071; http://dx.doi.org/10.4161/onci.23187
182. Kadota K, Nitadori JI, Adusumilli PS. Prognostic value of the immune microenvironment in lung adenocarcinoma. Oncoimmunology 2013; 2:e24036; PMID:23762792; http://dx.doi.org/10.4161/onci.24036
183. Fridman WH. The immune microenvironment as a guide for cancer therapies. Oncoimmunology 2012; 1:261-2; PMID:22737600; http://dx.doi.org/10.4161/onci.19651
184. Dick LR, Fleming PE. Building on bortezomib: second-generation proteasome inhibitors as anti-cancer therapy. Drug Discov Today 2010; 15:243-9; PMID:20116451; http://dx.doi.org/10.1016/j.drudis.2010.01.008
185. Gu JJ, Hernandez-Ilizaliturri FJ, Kaufman GP, Czuczman NM, Mavis C, Skitzki JJ, Czuczman MS. The novel proteasome inhibitor carfilzomib induces cell cycle arrest, apoptosis and potentiates the antitumour activity of chemotherapy in rituximab-resistant lymphoma. Br J Haematol 2013; 162:657-69; PMID:23826755; http://dx.doi.org/10.1111/bjh.12452
186. Hong YS, Hong SW, Kim SM, Jin DH, Shin JS, Yoon DH, Kim KP, Lee JL, Heo DS, Lee JS, et al. Bortezomib induces G2-M arrest in human colon cancer cells through ROS-inducible phosphorylation of ATM-CHK1. Int J Oncol 2012; 41:76-82; PMID:22552540; http://dx.doi.org/10.3892/ijo.2012.1448
187. Baiz D, Pozzato G, Dapas B, Farra R, Scaggiante B, Grassi M, Uxa L, Giansante C, Zennaro C, Guarnieri G, et al. Bortezomib arrests the proliferation of hepatocellular carcinoma cells HepG2 and JHH6 by differentially affecting E2F1, p21 and p27 levels. Biochimie 2009; 91:373-82; PMID:19041685; http://dx.doi.org/10.1016/j.biochi.2008.10.015
188. Ling YH, Liebes L, Jiang JD, Holland JF, Elliott PJ, Adams J, Muggia FM, Perez-Soler R. Mechanisms of proteasome inhibitor PS-341-induced G(2)-M-phase arrest and apoptosis in human non-small cell lung cancer cell lines. Clin Cancer Res 2003; 9:1145-54; PMID:12631620
189. Ling YH, Liebes L, Ng B, Buckley M, Elliott PJ, Adams J, Jiang JD, Muggia FM, Perez-Soler R. PS-341, a novel proteasome inhibitor, induces Bcl^{-}2 phosphorylation and cleavage in association with G2-M phase arrest and apoptosis. Mol Cancer Ther 2002; 1:841-9; PMID:12492117;
190. Miller CP, Ban K, Dujka ME, McConkey DJ, Munsell M, Palladino M, Chandra J. NPI-0052, a novel proteasome inhibitor, induces caspase-8 and ROS-dependent apoptosis alone and in combination with HDAC inhibitors in leukemia cells. Blood 2007; 110:267-77; PMID:17356134; http://dx.doi.org/10.1182/blood-2006-03-013128
191. Chari A, Mazumder A, Jagannath S. Proteasome inhibition and its therapeutic potential in multiple myeloma. Biologics 2010; 4:273-87; PMID:21116326
192. Kashkar H, Deggerich A, Seeger JM, Yazdanpanah B, Wiegmann K, Haubert D, Pongratz C, Krönke M. NF-kappaB-independent down-regulation of XIAP by bortezomib sensitizes HL B cells against cytotoxic drugs. Blood 2007; 109:3982-8; PMID:17185461; http://dx.doi.org/10.1182/blood-2006-10-053959
193. Goldberg AL. Development of proteasome inhibitors as research tools and cancer drugs. J Cell Biol 2012; 199:583-8; PMID:23148232; http://dx.doi.org/10.1083/jcb.201210077
194. Hideshima T, Chauhan D, Richardson P, Mitsiades C, Mitsiades N, Hayashi T, Munshi N, Dang L, Castro A, Palombella V, et al. NF-kappa B as a therapeutic target in multiple myeloma. J Biol Chem 2002; 277:16639-47; PMID:11872748; http://dx.doi.org/10.1074/jbc.M200360200
195. Palombella VJ, Rando OJ, Goldberg AL, Maniatis T. The ubiquitin-proteasome pathway is required for processing the NF-kappa B1 precursor protein and the activation of NF-kappa B. Cell 1994; 78:773-85; PMID:8087845; http://dx.doi.org/10.1016/S0092-8674(94)90482-0
196. Kuhnemuth B, Michl P. The role of CUX1 in antagonizing NF-kappaB signaling in TAMs. Oncoimmunology 2014; 3:e28270; PMID:25050198; http://dx.doi.org/10.4161/onci.28270
197. Nerini-Molteni S, Ferrarini M, Cozza S, Caligaris-Cappio F, Sitia R. Redox homeostasis modulates the sensitivity of myeloma cells to bortezomib. Br J Haematol 2008; 141:494-503; PMID:18341633; http://dx.doi.org/10.1111/j.1365-2141.2008.07066.x
198. Perez-Galan P, Roue G, Villamor N, Montserrat E, Campo E, Colomer D. The proteasome inhibitor bortezomib induces apoptosis in mantle-cell lymphoma through generation of ROS and Noxa activation independent of p53 status. Blood 2006; 107:257-64; PMID:16166592; http://dx.doi.org/10.1182/blood-2005-05-2091
199. Ling YH, Liebes L, Zou Y, Perez-Soler R. Reactive oxygen species generation and mitochondrial dysfunction in the apoptotic response to Bortezomib, a novel proteasome inhibitor, in human H460 non-small cell lung cancer cells. J Biol Chem 2003; 278:33714-23; PMID:12821677; http://dx.doi.org/10.1074/jbc.M302559200
200. Hideshima T, Mitsiades C, Akiyama M, Hayashi T, Chauhan D, Richardson P, Schlossman R, Podar K, Munshi NC, Mitsiades N, et al. Molecular mechanisms mediating antimyeloma activity of proteasome inhibitor PS-341. Blood 2003; 101:1530-4; PMID:12393500; http://dx.doi.org/10.1182/blood-2002-08-2543
201. Wang Q, Mora-Jensen H, Weniger MA, Perez-Galan P, Wolford C, Hai T, Ron D, Chen W, Trenkle W, Wiestner A, et al. ERAD inhibitors integrate ER stress with an epigenetic mechanism to activate BH3-only protein NOXA in cancer cells. Proc Natl Acad Sci U S A 2009; 106:2200-5; PMID:19164757; http://dx.doi.org/10.1073/pnas.0807611106
202. Obeng EA, Carlson LM, Gutman DM, Harrington WJ, Jr., Lee KP, Boise LH. Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. Blood 2006; 107:4907-16; PMID:16507771; http://dx.doi.org/10.1182/blood-2005-08-3531
203. Fribley A, Zeng Q, Wang CY. Proteasome inhibitor PS-341 induces apoptosis through induction of endoplasmic reticulum stress-reactive oxygen species in head and neck squamous cell carcinoma cells. Mol Cell Biol 2004; 24:9695-704; PMID:15509775; http://dx.doi.org/10.1128/MCB.24.22.9695-9704.2004
204. Michaud M, Sukkurwala AQ, Di Sano F, Zitvogel L, Kepp O, Kroemer G. Synthetic induction of immunogenic cell death by genetic stimulation of endoplasmic reticulum stress. Oncoimmunology 2014; 3: e28276; PMID:25050202; http://dx.doi.org/10.4161/onci.28276
205. Landowski TH, Megli CJ, Nullmeyer KD, Lynch RM, Dorr RT. Mitochondrial-mediated disregulation of Ca^{2+} is a critical determinant of Velcade (PS-341/bortezomib) cytotoxicity in myeloma cell lines. Cancer Res 2005; 65:3828-36; PMID:15867381; http://dx.doi.org/10.1158/0008-5472.CAN-04-3684
206. Cirone M, Di Renzo L, Lotti LV, Conte V, Trivedi P, Santarelli R, Gonnella R, Frati L, Faggioni A. Primary effusion lymphoma cell death induced by bortezomib and AG 490 activates dendritic cells through CD91. PLoS One 2012; 7:e31732; PMID:22412839; http://dx.doi.org/10.1371/journal.pone.0031732
207. Demaria S, Santori FR, Ng B, Liebes L, Formenti SC, Vukmanovic S. Select forms of tumor cell apoptosis induce dendritic cell maturation. J Leukoc Biol 2005; 77:361-8; PMID:15569694; http://dx.doi.org/10.1189/jlb.0804478
208. Spisek R, Charalambous A, Mazumder A, Vesole DH, Jagannath S, Dhodapkar MV. Bortezomib enhances dendritic cell (DC)-mediated induction of immunity to human myeloma via exposure of cell surface heat shock protein 90 on dying tumor cells: therapeutic implications. Blood 2007; 109:4839-45; PMID:17299090; http://dx.doi.org/10.1182/blood-2006-10-054221
209. Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol 2013; 31:51-72; PMID:23157435; http://dx.doi.org/10.1146/annurev-immunol-032712-100008
210. Galluzzi L, Senovilla L, Zitvogel L, Kroemer G. The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov 2012; 11:215-33; PMID:22301798; http://dx.doi.org/10.1038/nrd3626
211. Viel S, Charrier E, Marcais A, Rouzaire P, Bienvenu J, Karlin L, Salles G, Walzer T. Monitoring NK cell activity in patients with hematological malignancies. Oncoimmunology 2013; 2:e26011; PMID:24327939; http://dx.doi.org/10.4161/onci.26011
212. Nair JR, Rozanski CH, Lee KP. Under one roof: the bone marrow survival niche for multiple myeloma and normal plasma cells. Oncoimmunology 2012; 1:388-9; PMID:22737625; http://dx.doi.org/10.4161/onci.18746
213. Kisselev AF, van der Linden WA, Overkleeft HS. Proteasome inhibitors: an expanding army attacking a unique target. Chem Biol 2012; 19:99-115; PMID:22284358; http://dx.doi.org/10.1016/j.chembiol.2012.01.003
214. Borissenko L, Groll M. 20S proteasome and its inhibitors: crystallographic knowledge for drug development. Chem Rev 2007; 107:687-717; PMID:17316053; http://dx.doi.org/10.1021/cr0502504

215. Groll M, Berkers CR, Ploegh HL, Ovaa H. Crystal structure of the boronic acid-based proteasome inhibitor bortezomib in complex with the yeast 20S proteasome. Structure 2006; 14:451-6; PMID:16531229; http://dx.doi.org/10.1016/j.str.2005.11.019
216. Adams J. The development of proteasome inhibitors as anticancer drugs. Cancer Cell 2004; 5:417-21; PMID:15144949; http://dx.doi.org/10.1016/S1535-6108(04)00120-5
217. LeBlanc R, Catley LP, Hideshima T, Lentzsch S, Mitsiades CS, Mitsiades N, Neuberg D, Goloubeva O, Pien CS, Adams J, et al. Proteasome inhibitor PS-341 inhibits human myeloma cell growth in vivo and prolongs survival in a murine model. Cancer Res 2002; 62:4996-5000; PMID:12208752
218. Shah SA, Potter MW, McDade TP, Ricciardi R, Perugini RA, Elliott PJ, Adams J, Callery MP. 26S proteasome inhibition induces apoptosis and limits growth of human pancreatic cancer. J Cell Biochem 2001; 82:110-22; PMID:11400168; http://dx.doi.org/10.1002/jcb.1150
219. Sunwoo JB, Chen Z, Dong G, Yeh N, Crowl Bancroft C, Sausville E, Adams J, Elliott P, Van Waes C. Novel proteasome inhibitor PS-341 inhibits activation of nuclear factor-kappa B, cell survival, tumor growth, and angiogenesis in squamous cell carcinoma. Clin Cancer Res 2001; 7:1419-28; PMID:11350913
220. Hideshima T, Richardson P, Chauhan D, Palombella VJ, Elliott PJ, Adams J, Anderson KC. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res 2001; 61:3071-6; PMID:11306489
221. Hideshima T, Richardson PG, Anderson KC. Mechanism of action of proteasome inhibitors and deacetylase inhibitors and the biological basis of synergy in multiple myeloma. Mol Cancer Ther 2011; 10:2034-42; PMID:22072815; http://dx.doi.org/10.1158/1535-7163.MCT-11-0433
222. Boccadoro M, Morgan G, Cavenagh J. Preclinical evaluation of the proteasome inhibitor bortezomib in cancer therapy. Cancer Cell Int 2005; 5:18; PMID:15929791; http://dx.doi.org/10.1186/1475-2867-5-18
223. Reddy N, Czuczman MS. Enhancing activity and overcoming chemoresistance in hematologic malignancies with bortezomib: preclinical mechanistic studies. Ann Oncol 2010; 21:1756-64; PMID:20133382; http://dx.doi.org/10.1093/annonc/mdq009
224. Shah JJ, Orlowski RZ. Proteasome inhibitors in the treatment of multiple myeloma. Leukemia 2009; 23:1964-79; PMID:19741722; http://dx.doi.org/10.1038/leu.2009.173
225. Orlowski RZ. Bortezomib in combination with other therapies for the treatment of multiple myeloma. J Natl Compr Canc Netw 2004; 2 Suppl 4:S16-20; PMID:19791424
226. Mitsiades N, Mitsiades CS, Richardson PG, Poulaki V, Tai YT, Chauhan D, Fanourakis G, Gu X, Bailey C, Joseph M, et al. The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications. Blood 2003; 101:2377-80; PMID:12424198; http://dx.doi.org/10.1182/blood-2002-06-1768
227. Papandreou CN, Daliani DD, Nix D, Yang H, Madden T, Wang X, Pien CS, Millikan RE, Tu SM, Pagliaro L, et al. Phase I trial of the proteasome inhibitor bortezomib in patients with advanced solid tumors with observations in androgen-independent prostate cancer. J Clin Oncol 2004; 22:2108-21; PMID:15169797; http://dx.doi.org/10.1200/JCO.2004.02.106
228. Orlowski RZ, Stinchcombe TE, Mitchell BS, Shea TC, Baldwin AS, Stahl S, Adams J, Esseltine DL, Elliott PJ, Pien CS, et al. Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. J Clin Oncol 2002; 20:4420-7; PMID:12431963; http://dx.doi.org/10.1200/JCO.2002.01.133
229. Aghajanian C, Soignet S, Dizon DS, Pien CS, Adams J, Elliott PJ, Sabbatini P, Miller V, Hensley ML, Pezzulli S, et al. A phase I trial of the novel proteasome inhibitor PS341 in advanced solid tumor malignancies. Clin Cancer Res 2002; 8:2505-11; PMID:12171876
230. Auphan N, DiDonato JA, Rosette C, Helmberg A, Karin M. Immunosuppression by glucocorticoids: inhibition of NF-kappa B activity through induction of I kappa B synthesis. Science 1995; 270:286-90; PMID:7569976; http://dx.doi.org/10.1126/science.270.5234.286
231. Rinehart J, Keville L, Neidhart J, Wong L, DiNunno L, Kinney P, Aberle M, Tadlock L, Cloud G. Hematopoietic protection by dexamethasone or granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients treated with carboplatin and ifosfamide. Am J Clin Oncol 2003; 26:448-58; PMID:14528069; http://dx.doi.org/10.1097/01.coc.0000027268.23258.7D
232. Gaynon PS, Carrel AL. Glucocorticosteroid therapy in childhood acute lymphoblastic leukemia. Adv Exp Med Biol 1999; 457:593-605; PMID:10500839; http://dx.doi.org/10.1007/978-1-4615-4811-9_66
233. Hsu A, Ritchie DS, Neeson P. Are the immuno-stimulatory properties of Lenalidomide extinguished by co-administration of Dexamethasone? Oncoimmunology 2012; 1:372-4; PMID:22737619; http://dx.doi.org/10.4161/onci.18963
234. Richardson PG, Sonneveld P, Schuster M, Irwin D, Stadtmauer E, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. Blood 2007; 110:3557-60; PMID:17690257; http://dx.doi.org/10.1182/blood-2006-08-036947
235. Ranney HM, Gellhorn A. The effect of massive prednisone and prednisolone therapy on acute leukemia and malignant lymphomas. Am J Med 1957; 22:405-13; PMID:13402792; http://dx.doi.org/10.1016/0002-9343(57)90096-7
236. Gornati D, Zaffaroni N, Villa R, De Marco C, Silvestrini R. Modulation of melphalan and cisplatin cytotoxicity in human ovarian cancer cells resistant to alkylating drugs. Anticancer Drugs 1997; 8:509-16; PMID:9215615; http://dx.doi.org/10.1097/00001813-199706000-00014
237. Mateos MV, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, Spicka I, Petrucci MT, Palumbo A, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol 2010; 28:2259-66; PMID:20368561; http://dx.doi.org/10.1200/JCO.2009.26.0638
238. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, Spicka I, Petrucci MT, Palumbo A, Samoilova OS, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008; 359:906-17; PMID:18753647; http://dx.doi.org/10.1056/NEJMoa0801479
239. San-Miguel J, Blade J, Shpilberg O, Grosicki S, Maloisel F, Min CK, Polo Zarzuela M, Robak T, Prasad SV, Tee Goh Y, et al. Phase 2 randomized study of bortezomib-melphalan-prednisone with or without siltuximab (anti-IL-6) in multiple myeloma. Blood 2014; 123:4136-42; PMID:24833354; http://dx.doi.org/10.1182/blood-2013-12-546374
240. Mateos MV, Bringhen S, Richardson PG, Lahuerta JJ, Larocca A, Oriol A, Boccadoro M, García-Sanz R, Di Raimondo F, Esseltine DL, et al. Bortezomib cumulative dose, efficacy, and tolerability with three different bortezomib-melphalan-prednisone regimens in previously untreated myeloma patients ineligible for high-dose therapy. Haematologica 2014; 99:1114-22; PMID:24763402; http://dx.doi.org/10.3324/haematol.2013.099341
241. Ogawa Y, Suzuki K, Sakai A, Iida S, Ogura M, Tobinai K, Matsumoto M, Matsue K, Terui Y, Ohashi K, et al. Phase I/II study of bortezomib-melphalan-prednisolone for previously untreated Japanese patients with multiple myeloma. Cancer Sci 2013; 104:912-9; PMID:23574271; http://dx.doi.org/10.1111/cas.12172
242. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, Spicka I, Petrucci MT, Palumbo A, Samoilova OS, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. J Clin Oncol 2013; 31:448-55; PMID:23233713; http://dx.doi.org/10.1200/JCO.2012.41.6180
243. Petrucci MT, Levi A, Bringhen S, Scotti S, Gentilini F, Russo S, Siniscalchi A, Larocca A, Grammatico S, Boccadoro M, et al. Bortezomib, melphalan, and prednisone in elderly patients with relapsed/refractory multiple myeloma: a multicenter, open label phase 1/2 study. Cancer 2013; 119:971-7; PMID:23096113; http://dx.doi.org/10.1002/cncr.27820
244. Mateos MV, Oriol A, Martinez-Lopez J, Gutierrez N, Teruel AI, Lopez de la Guia A, López J, Bengoechea E, Pérez M, Polo M, et al. Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. Blood 2012; 120:2581-8; PMID:22889759; http://dx.doi.org/10.1182/blood-2012-05-427815
245. Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, Offidani M, Patriarca F, Nozzoli C, Guglielmelli T, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol 2010; 28:5101-9; PMID:20940200; http://dx.doi.org/10.1200/JCO.2010.29.8216
246. Mateos MV, Oriol A, Martinez-Lopez J, Gutierrez N, Teruel AI, de Paz R, García-Laraña J, Bengoechea E, Martín A, Mediavilla JD, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncol 2010; 11:934-41; PMID:20739218; http://dx.doi.org/10.1016/S1470-2045(10)70187-X
247. Ribrag V, Tilly H, Casasnovas O, Bosly A, Bouabdallah R, Delarue R, Boue F, Bron D, Feugier P, Haioun C, et al. Efficacy and toxicity of two schedules of bortezomib in patients with recurrent or refractory follicular lymphoma: a randomised phase II trial from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). Eur J Cancer 2013; 49:904-10; PMID:23273434; http://dx.doi.org/10.1016/j.ejca.2012.11.015
248. Gravelle P, Jean C, Valleron W, Laurent G, Fournie JJ. Innate predisposition to immune escape in follicular lymphoma cells. Oncoimmunology 2012; 1:555-6; PMID:22754785; http://dx.doi.org/10.4161/onci.19365
249. Delforge M, Blade J, Dimopoulos MA, Facon T, Kropff M, Ludwig H, Palumbo A, Van Damme P, San-Miguel JF, Sonneveld P. Treatment-related peripheral neuropathy in multiple myeloma: the challenge continues. Lancet Oncol 2010; 11:1086-95; PMID:20932799; http://dx.doi.org/10.1016/S1470-2045(10)70068-1
250. San Miguel J, Blade J, Boccadoro M, Cavenagh J, Glasmacher A, Jagannath S, Lonial S, Orlowski RZ, Sonneveld P, Ludwig H. A practical update on the use

of bortezomib in the management of multiple myeloma. Oncologist 2006; 11:51-61; PMID:16401713; http://dx.doi.org/10.1634/theon-cologist.11-1-51
251. Richardson PG, Briemberg H, Jagannath S, Wen PY, Barlogie B, Berenson J, Singhal S, Siegel DS, Irwin D, Schuster M, et al. Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. J Clin Oncol 2006; 24:3113-20; PMID:16754936; http://dx.doi.org/10.1200/JCO.2005.04.7779
252. Jagannath S, Durie BG, Wolf JL, Camacho ES, Irwin D, Lutzky J, McKinley M, Potts P, Gabayan AE, Mazumder A, et al. Extended follow-up of a phase 2 trial of bortezomib alone and in combination with dexamethasone for the frontline treatment of multiple myeloma. Br J Haematol 2009; 146:619-26; PMID:19622094; http://dx.doi.org/10.1111/j.1365-2141.2009.07803.x
253. Mikhael JR, Belch AR, Prince HM, Lucio MN, Maiolino A, Corso A, Petrucci MT, Musto P, Komarnicki M, Stewart AK. High response rate to bortezomib with or without dexamethasone in patients with relapsed or refractory multiple myeloma: results of a global phase 3b expanded access program. Br J Haematol 2009; 144:169-75; PMID:19036114; http://dx.doi.org/10.1111/j.1365-2141.2008.07409.x
254. Jagannath S, Durie BG, Wolf J, Camacho E, Irwin D, Lutzky J, McKinley M, Gabayan E, Mazumder A, Schenkein D, et al. Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. Br J Haematol 2005; 129:776-83; PMID:15953004; http://dx.doi.org/10.1111/j.1365-2141.2005.05540.x
255. Montefusco V, Spina F, Patriarca F, Offidani M, Bruno B, Montanari M, Mussetti A, Sperotto A, Scortechini I, Dodero A, et al. Bortezomib plus dexamethasone followed by escalating donor lymphocyte infusions for patients with multiple myeloma relapsing or progressing after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2013; 19:424-8; PMID:23142330; http://dx.doi.org/10.1016/j.bbmt.2012.10.032
256. Aranda F, Vacchelli E, Obrist F, Eggermont A, Galon J, Herve Fridman W, Cremer I, Tartour E, Zitvogel L, Kroemer G, et al. Trial Watch: adoptive cell transfer for anticancer immunotherapy. Oncoimmunology 2014; 3:e28344; PMID:25050207; http://dx.doi.org/10.4161/onci.28344
257. Vacchelli E, Eggermont A, Fridman WH, Galon J, Tartour E, Zitvogel L, Kroemer G, Galluzzi L, et al. Trial Watch: adoptive cell transfer for anticancer immunotherapy. Oncoimmunology 2013; 2:e24238; PMID:23762803; http://dx.doi.org/10.4161/onci.24238
258. Manzo T, Michelini RH, Sturmheit T, Basso V, Bellone M, Mondino A. Tumor-targeting vaccination instructs graft-vs.-tumor immune responses. Oncoimmunology 2013; 2:e25996; PMID:24244899; http://dx.doi.org/10.4161/onci.25996
259. Tyler EM, Koehne G. The emergence of WT1-specific T-cell responses following allogeneic T cell-depleted hematopoietic stem cell transplantation and low-dose donor lymphocyte infusions is associated with a graft-vs.- myeloma effect. Oncoimmunology 2013; 2:e24963; PMID:24073375; http://dx.doi.org/10.4161/onci.24963
260. Vacchelli E, Senovilla L, Eggermont A, Fridman WH, Galon J, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: chemotherapy with immunogenic cell death inducers. Oncoimmunology 2013; 2:e23510; PMID:23687621; http://dx.doi.org/10.4161/onci.23510
261. Alizadeh D, Katsanis E, Larmonier N. Chemotherapeutic targeting of myeloid-derived suppressor cells. Oncoimmunology 2014; 3:e27359; PMID:24653963; http://dx.doi.org/10.4161/onci.27359
262. Ma Y, Adjemian S, Yang H, Catani JP, Hannani D, Martins I, Michaud M, Kepp O, Sukkurwala AQ, Vacchelli E, et al. ATP-dependent recruitment, survival and differentiation of dendritic cell precursors in the tumor bed after anticancer chemotherapy. Oncoimmunology 2013; 2:e24568; PMID:23894718
263. Orlowski RZ, Nagler A, Sonneveld P, Blade J, Hajek R, Spencer A, San Miguel J, Robak T, Dmoszynska A, Horvath N, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol 2007; 25:3892-901; PMID:17679727; http://dx.doi.org/10.1200/JCO.2006.10.5460
264. Orlowski RZ, Voorhees PM, Garcia RA, Hall MD, Kudrik FJ, Allred T, Johri AR, Jones PE, Ivanova A, Van Deventer HW, et al. Phase 1 trial of the proteasome inhibitor bortezomib and pegylated liposomal doxorubicin in patients with advanced hematologic malignancies. Blood 2005; 105:3058-65; PMID:15626743; http://dx.doi.org/10.1182/blood-2004-07-2911
265. Takamatsu Y, Sunami K, Muta T, Morimoto H, Miyamoto T, Higuchi M, Uozumi K, Hata H, Tamura K; Kyushu Hematology Organization for Treatment Study Group (K-HOT). Bortezomib, doxorubicin and intermediate-dose dexamethasone (iPAD) therapy for relapsed or refractory multiple myeloma: a multicenter phase 2 study. Int J Hematol 2013; 98:179-85; PMID:23832805; http://dx.doi.org/10.1007/s12185-013-1389-6
266. Popat R, Oakervee HE, Hallam S, Curry N, Odeh L, Foot N, Esseltine DL, Drake M, Morris C, Cavenagh JD. Bortezomib, doxorubicin and dexamethasone (PAD) front-line treatment of multiple myeloma: updated results after long-term follow-up. Br J Haematol 2008; 141:512-6; PMID:18371113; http://dx.doi.org/10.1111/j.1365-2141.2008.06997.x
267. Oakervee HE, Popat R, Curry N, Smith P, Morris C, Drake M, Agrawal S, Stec J, Schenkein D, Esseltine DL, et al. PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. Br J Haematol 2005; 129:755-62; PMID:15953001; http://dx.doi.org/10.1111/j.1365-2141.2005.05519.x
268. Dimopoulos M, Siegel DS, Lonial S, Qi J, Hajek R, Facon T, Rosinol L, Williams C, Blacklock H, Goldschmidt H, et al. Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): a multicentre, randomised, double-blind study. Lancet Oncol 2013; 14:1129-40; PMID:24055414; http://dx.doi.org/10.1016/S1470-2045(13)70398-X
269. San-Miguel JF, Richardson PG, Gunther A, Sezer O, Siegel D, Blade J, LeBlanc R, Sutherland H, Sopala M, Mishra KK, et al. Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol 2013; 31:3696-703; PMID:24019544; http://dx.doi.org/10.1200/JCO.2012.46.7068
270. Richardson PG, Schlossman RL, Alsina M, Weber DM, Coutre SE, Gasparetto C, Mukhopadhyay S, Ondovik MS, Khan M, Paley CS, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood 2013; 122:2331-7; PMID:23950178; http://dx.doi.org/10.1182/blood-2013-01-481325
271. Adamopoulou E, Naumann U. HDAC inhibitors and their potential applications to glioblastoma therapy. Oncoimmunology 2013; 2:e25219; PMID:24167760; http://dx.doi.org/10.4161/onci.25219
272. Shen L, Pili R. Class I histone deacetylase inhibition is a novel mechanism to target regulatory T cells in immunotherapy. Oncoimmunology 2012; 1:948-50; PMID:23162767; http://dx.doi.org/10.4161/onci.20306
273. Zitvogel G, Proietti E, Moschella F. The Janus face of cyclophosphamide: a sterile inflammatory response that potentiates cancer immunotherapy. Oncoimmunology 2013; 2:e25789; PMID:24244905; http://dx.doi.org/10.4161/onci.25789
274. Walter S, Weinschenk T, Reinhardt C, Singh-Jasuja H. Single-dose cyclophosphamide synergizes with immune responses to the renal cell cancer vaccine IMA901. Oncoimmunology 2013; 2:e22246; PMID:23482454; http://dx.doi.org/10.4161/onci.22246
275. Chen X, Wakefield LM, Oppenheim JJ. Synergistic antitumor effects of a TGFbeta inhibitor and cyclophosphamide. Oncoimmunology 2014; 3:e28247; PMID:25050195; http://dx.doi.org/10.4161/onci.28247
276. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, Di Raimondo F, Crippa C, Zamagni E, Palumbo A, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet 2010; 376:2075-85; PMID:21146205; http://dx.doi.org/10.1016/S0140-6736(10)61424-9
277. Ludwig H, Viterbo L, Greil R, Masszi T, Spicka I, Shpilberg O, Hajek R, Dmoszynska A, Paiva B, Vidriales MB, et al. Randomized phase II study of bortezomib, thalidomide, and dexamethasone with or without cyclophosphamide as induction therapy in previously untreated multiple myeloma. J Clin Oncol 2013; 31:247-55; PMID:23091109; http://dx.doi.org/10.1200/JCO.2011.39.5137
278. Richardson PG, Xie W, Jagannath S, Jakubowiak A, Lonial S, Raje NS, Alsina M, Ghobrial IM, Schlossman RL, Munshi NC, et al. A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma. Blood 2014; 123:1461-9; PMID:24429336; http://dx.doi.org/10.1182/blood-2013-07-517276
279. Andhavarapu S, Roy V. Immunomodulatory drugs in multiple myeloma. Expert Rev Hematol 2013; 6:69-82; PMID:23373782; http://dx.doi.org/10.1586/ehm.12.62
280. Rummel MJ, Gregory SA. Bendamustine's emerging role in the management of lymphoid malignancies. Semin Hematol 2011; 48 Suppl 1:S24-36; PMID:21530769; http://dx.doi.org/10.1053/j.seminhematol.2011.03.004
281. Leoni LM, Hartley JA. Mechanism of action: the unique pattern of bendamustine-induced cytotoxicity. Semin Hematol 2011; 48 Suppl 1:S12-23; PMID:21530768; http://dx.doi.org/10.1053/j.seminhematol.2011.03.003
282. Litterman AJ, Dudek AZ, Largaespada DA. Alkylating chemotherapy may exert a uniquely deleterious effect upon neo-antigen-targeting anticancer vaccination. Oncoimmunology 2013; 2:e26294; PMID:24251080; http://dx.doi.org/10.4161/onci.26294
283. Vacchelli E, Eggermont A, Galon J, Sautes-Fridman C, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: monoclonal antibodies in cancer therapy. Oncoimmunology 2013; 2:e22789; PMID:23482847
284. Offidani M, Corvatta L, Maracci L, Liberati AM, Ballanti S, Attolico I, Caraffa P, Alesiani F, Caravita di Toritto T, Gentili S, et al. Efficacy and tolerability of bendamustine, bortezomib and dexamethasone in patients with relapsed-refractory multiple myeloma: a phase II study. Blood Cancer J 2013; 3:e162; PMID:24270324; http://dx.doi.org/10.1038/bcj.2013.58
285. Ludwig H, Kasparu H, Leitgeb C, Rauch E, Linkesch W, Zojer N, Greil R, Seebacher A, Pour L, Weißmann A, et al. Bendamustine-bortezomib-dexamethasone is an active and well-tolerated regimen in patients with relapsed or refractory multiple myeloma.

Blood 2014; 123:985-91; PMID:24227817; http://dx.doi.org/10.1182/blood-2013-08-521468
286. Berenson JR, Yellin O, Bessudo A, Boccia RV, Noga SJ, Gravenor DS, Patel-Donnelly D, Siegel RS, Kewalramani T, Gorak EJ, et al. Phase I/II trial assessing bendamustine plus bortezomib combination therapy for the treatment of patients with relapsed or refractory multiple myeloma. Br J Haematol 2013; 160:321-30; PMID:23150919; http://dx.doi.org/10.1111/bjh.12129
287. White D, Kassim A, Bhaskar B, Yi J, Wamstad K, Paton VE. Results from AMBER, a randomized phase 2 study of bevacizumab and bortezomib versus bortezomib in relapsed or refractory multiple myeloma. Cancer 2013; 119:339-47; PMID:22811009; http://dx.doi.org/10.1002/cncr.27745
288. Mansfield AS, Nevala WK, Lieser EA, Leontovich AA, Markovic SN. The immunomodulatory effects of bevacizumab on systemic immunity in patients with metastatic melanoma. Oncoimmunology 2013; 2: e24436; PMID:23762809
289. Foy KC, Miller MJ, Moldovan N, Carson Iii WE, Kaumaya PT. Combined vaccination with HER-2 peptide followed by therapy with VEGF peptide mimics exerts effective anti-tumor and anti-angiogenic effects in vitro and in vivo. Oncoimmunology 2012; 1:1048-60; PMID:23170253; http://dx.doi.org/10.4161/onci.20708
290. Quereux G, Dreno B. Fotemustine for the treatment of melanoma. Expert Opin Pharmacother 2011; 12:2891-904; PMID:22077794; http://dx.doi.org/10.1517/14656566.2011.633513
291. Jacquillat C, Khayat D, Banzet P, Weil M, Fumoleau P, Avril MF, Namer M, Bonneterre J, Kerbrat P, Bonerandi JJ, et al. Final report of the French multicenter phase II study of the nitrosourea fotemustine in 153 evaluable patients with disseminated malignant melanoma including patients with cerebral metastases. Cancer 1990; 66:1873-8; PMID:2224783
292. Mangiacavalli S, Pochintesta L, Pascutto C, Cocito F, Pompa A, Cazzola M, Corso A. Good clinical activity and favorable toxicity profile of once weekly bortezomib, fotemustine, and dexamethasone (B-MuD) for the treatment of relapsed multiple myeloma. Am J Hematol 2013; 88:102-6; PMID:23224960; http://dx.doi.org/10.1002/ajh.23358
293. Gribben JG, O'Brien S. Update on therapy of chronic lymphocytic leukemia. J Clin Oncol 2011; 29:544-50; PMID:21220603; http://dx.doi.org/10.1200/JCO.2010.32.3865
294. Rai KR, Peterson BL, Appelbaum FR, Kolitz J, Elias L, Shepherd L, Hines J, Threatte GA, Larson RA, Cheson BD, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med 2000; 343:1750-7; PMID:11114313; http://dx.doi.org/10.1056/NEJM200012143432402
295. Caballero-Velazquez T, Lopez-Corral L, Encinas C, Castilla-Llorente C, Martino R, Rosinol L, Sampol A, Caballero D, Serrano D, Heras I, et al. Phase II clinical trial for the evaluation of bortezomib within the reduced intensity conditioning regimen (RIC) and post-allogeneic transplantation for high-risk myeloma patients. Br J Haematol 2013; 162:474-82; PMID:23772672; http://dx.doi.org/10.1111/bjh.12410
296. Gay F, Magarotto V, Crippa C, Pescosta N, Guglielmelli T, Cavallo F, Pezzatti S, Ferrari S, Liberati AM, Oliva S, et al. Bortezomib induction, reduced-intensity transplantation, and lenalidomide consolidation-maintenance for myeloma: updated results. Blood 2013; 122:1376-83; PMID:23775712; http://dx.doi.org/10.1182/blood-2013-02-483073
297. Kouroukis CT, Fernandez LA, Crump M, Gascoyne RD, Chua NS, Buckstein R, Turner R, Assouline S, Klasa RJ, Walsh W, et al. A phase II study of bortezomib and gemcitabine in relapsed mantle cell lymphoma from the National Cancer Institute of Canada Clinical Trials Group (IND 172). Leuk Lymphoma 2011; 52:394-9; PMID:21323520; http://dx.doi.org/10.3109/10428194.2010.546015
298. Gujar SA, Clements D, Lee PW. Two is better than one: complementing oncolytic virotherapy with gemcitabine to potentiate antitumor immune responses. Oncoimmunology 2014; 3:e27622; PMID:24804161
299. Amit M, Gil Z. Macrophages increase the resistance of pancreatic adenocarcinoma cells to gemcitabine by upregulating cytidine deaminase. Oncoimmunology 2013; 2:e27231; PMID:24498570
300. Natarajan-Ame S, Park S, Ades L, Vey N, Guerci-Bresler A, Cahn JY, Etienne G, Bordessoule D, Ravoet C, Legros L, et al. Bortezomib combined with low-dose cytarabine in Intermediate-2 and high risk myelodysplastic syndromes. A phase I/II Study by the GFM. Br J Haematol 2012; 158:232-7; PMID:22571447; http://dx.doi.org/10.1111/j.1365-2141.2012.09153.x
301. Thepot S, Lainey E, Cluzeau T, Sebert M, Leroy C, Ades L, Tailler M, Galluzzi L, Baran-Marszak F, Roudot H, et al. Hypomethylating agents reactivate FOXO3A in acute myeloid leukemia. Cell Cycle 2011; 10:2323-30; PMID:21654193; http://dx.doi.org/10.4161/cc.10.14.16399
302. Boehrer S, Ades L, Braun T, Galluzzi L, Grosjean J, Fabre C, Le Roux G, Gardin C, Martin A, de Botton S, et al. Erlotinib exhibits antineoplastic off-target effects in AML and MDS: a preclinical study. Blood 2008; 111:2170-80; PMID:17925489; http://dx.doi.org/10.1182/blood-2007-07-100362
303. Roy R, Evens AM, Patton D, Gallot L, Larson A, Rademaker A, Cilley J, Spies S, Variakojis D, Gordon LI, et al. Bortezomib may be safely combined with Y-90-ibritumomab tiuxetan in patients with relapsed/refractory follicular non-Hodgkin lymphoma: a phase I trial of combined induction therapy and bortezomib consolidation. Leuk Lymphoma 2013; 54:497-502; PMID:22906230; http://dx.doi.org/10.3109/10428194.2012.722215
304. Galluzzi L, Kepp O, Kroemer G. Immunogenic cell death in radiation therapy. Oncoimmunology 2013; 2:e26536
305. Vacchelli E, Vitale I, Tartour E, Eggermont A, Sautes-Fridman C, Galon J, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: anticancer radioimmunotherapy. Oncoimmunology 2013; 2:e25595; PMID:24319634
306. Evens AM, Smith MR, Lossos IS, Helenowski I, Millenson M, Winter JN, Rosen ST, Gordon LI. Frontline bortezomib and rituximab for the treatment of newly diagnosed high tumour burden indolent non-hodgkin lymphoma: a multicentre phase II study. Br J Haematol 2014; PMID:24761968; http://dx.doi.org/10.1111/bjh.12915.
307. Fowler N, Kahl BS, Lee P, Matous JV, Cashen AF, Jacobs SA, Letzer J, Amin B, Williams ME, Smith S, et al. Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: the phase II VERTICAL study. J Clin Oncol 2011; 29:3389-95; PMID:21810687; http://dx.doi.org/10.1200/JCO.2010.32.1844
308. Ruan J, Martin P, Furman RR, Lee SM, Cheung K, Vose JM, Lacasce A, Morrison J, Elstrom R, Ely S, et al. Bortezomib plus CHOP-rituximab for previously untreated diffuse large B-cell lymphoma and mantle cell lymphoma. J Clin Oncol 2011; 29:690-7; PMID:21189393; http://dx.doi.org/10.1200/JCO.2010.31.1142
309. Bruserud O, Reikvam H, Kittang AO, Ahmed AB, Tvedt TH, Sjo M, Hatfield KJ. High-dose etoposide in allogeneic stem cell transplantation. Cancer Chemother Pharmacol 2012; 70:765-82; PMID:23053272; http://dx.doi.org/10.1007/s00280-012-1990-z
310. Montecucco A, Biamonti G. Cellular response to etoposide treatment. Cancer Lett 2007; 252:9-18; PMID:17166655; http://dx.doi.org/10.1016/j.canlet.2006.11.005
311. William BM, Allen MS, Loberiza FR, Jr., Bociek RG, Bierman PJ, Armitage JO, Vose JM. Phase I/II study of bortezomib-BEAM and autologous hematopoietic stem cell transplantation for relapsed indolent non-Hodgkin lymphoma, transformed, or mantle cell lymphoma. Biol Blood Marrow Transplant 2014; 20:536-42; PMID:24434781; http://dx.doi.org/10.1016/j.bbmt.2014.01.004
312. Evens AM, Rosen ST, Helenowski I, Kline J, Larsen A, Colvin J, Winter JN, van Besien KM, Gordon LI, Smith SM. A phase I/II trial of bortezomib combined concurrently with gemcitabine for relapsed or refractory DLBCL and peripheral T-cell lymphomas. Br J Haematol 2013; 163:55-61; PMID:23927371; http://dx.doi.org/10.1111/bjh.12488
313. Schelman WR, Traynor AM, Holen KD, Kolesar JM, Attia S, Hoang T, Eickhoff J, Jiang Z, Alberti D, Marnocha R, et al. A phase I study of vorinostat in combination with bortezomib in patients with advanced malignancies. Invest New Drugs 2013; 31:1539-46; PMID:24114121; http://dx.doi.org/10.1007/s10637-013-0029-6
314. Kumar SK, Jett J, Marks R, Richardson R, Quevedo F, Moynihan T, Croghan G, Markovic SN, Bible KC, Qin R, et al. Phase 1 study of sorafenib in combination with bortezomib in patients with advanced malignancies. Invest New Drugs 2013; 31:1201-6; PMID:23887852; http://dx.doi.org/10.1007/s10637-013-0004-2
315. Turkington RC, Purcell C, James CR, Millar J, Napier E, Law D, Gallagher R, Morris M, Wilson RH, Eatock MM. A phase I trial of bortezomib in combination with epirubicin, carboplatin and capecitabine (ECarboX) in advanced oesophagogastric adenocarcinoma. Invest New Drugs 2014; 32:250-60; PMID:23665866; http://dx.doi.org/10.1007/s10637-013-9970-7
316. Schenk E, Hendrickson AE, Northfelt D, Toft DO, Ames MM, Menefee M, Satele D, Qin R, Erlichman C. Phase I study of tanespimycin in combination with bortezomib in patients with advanced solid malignancies. Invest New Drugs 2013; 31:1251-6; PMID:23543109; http://dx.doi.org/10.1007/s10637-013-9946-7
317. Harvey RD, Owonikoko TK, Lewis CM, Akintayo A, Chen Z, Tighiouart M, Ramalingam SS, Fanucchi MP, Nadella P, Rogatko A, et al. A phase 1 Bayesian dose selection study of bortezomib and sunitinib in patients with refractory solid tumor malignancies. Br J Cancer 2013; 108:762-5; PMID:23322195; http://dx.doi.org/10.1038/bjc.2012.604
318. Kubicek GJ, Axelrod RS, Machtay M, Ahn PH, Anne PR, Fogh S, Cognetti D, Myers TJ, Curran WJ Jr, Dicker AP. Phase I trial using the proteasome inhibitor bortezomib and concurrent chemoradiotherapy for head-and-neck malignancies. Int J Radiat Oncol Biol Phys 2012; 83:1192-7; PMID:22245208; http://dx.doi.org/10.1016/j.ijrobp.2011.09.023
319. Deming DA, Ninan J, Bailey HH, Kolesar JM, Eickhoff J, Reid JM, Ames MM, McGovern RM, Alberti D, Marnocha R, et al. A Phase I study of intermittently dosed vorinostat in combination with bortezomib in patients with advanced solid tumors. Invest New Drugs 2014; 32:323-9; PMID:24114123; http://dx.doi.org/10.1007/s10637-013-0035-8
320. Kobrinsky B, Joseph SO, Muggia F, Liebes L, Beric A, Malankar A, Ivy P, Hochster H. A phase I and pharmacokinetic study of oxaliplatin and bortezomib: activity, but dose-limiting neurotoxicity. Cancer Chemother Pharmacol 2013; 72:1073-8; PMID:24048674; http://dx.doi.org/10.1007/s00280-013-2295-6
321. Poklepovic A, Youssefian LE, Winning M, Birdsell CA, Crosby NA, Ramakrishnan V, Ernstoff MS, Roberts JD. Phase I trial of bortezomib and dacarbazine in melanoma and soft tissue sarcoma. Invest New Drugs 2013; 31:937-42; PMID:23315028; http://dx.doi.org/10.1007/s10637-012-9913-8

322. Jones DR, Moskaluk CA, Gillenwater HH, Petroni GR, Burks SG, Philips J, Rehm PK, Olazagasti J, Kozower BD, Bao Y. Phase I trial of induction histone deacetylase and proteasome inhibition followed by surgery in non-small-cell lung cancer. J Thorac Oncol 2012; 7:1683-90; PMID:23059775; http://dx.doi.org/10.1097/JTO.0b013e318267928d
323. Li T, Ho L, Piperdi B, Elrafei T, Camacho FJ, Rigas JR, Perez-Soler R, Gucalp R. Phase II study of the proteasome inhibitor bortezomib (PS-341, Velcade) in chemotherapy-naive patients with advanced stage non-small cell lung cancer (NSCLC). Lung Cancer 2010; 68:89-93; PMID:19524318; http://dx.doi.org/10.1016/j.lungcan.2009.05.009
324. Shah MA, Power DG, Kindler HL, Holen KD, Kemeny MM, Ilson DH, Tang L, Capanu M, Wright JJ, Kelsen DP. A multicenter, phase II study of bortezomib (PS-341) in patients with unresectable or metastatic gastric and gastroesophageal junction adenocarcinoma. Invest New Drugs 2011; 29:1475-81; PMID:20574790; http://dx.doi.org/10.1007/s10637-010-9474-7
325. Kim GP, Mahoney MR, Szydlo D, Mok TS, Marshke R, Holen K, Picus J, Boyer M, Pitot HC, Rubin J, et al. An international, multicenter phase II trial of bortezomib in patients with hepatocellular carcinoma. Invest New Drugs 2012; 30:387-94; PMID:20839030; http://dx.doi.org/10.1007/s10637-010-9532-1
326. Denlinger CS, Meropol NJ, Li T, Lewis NL, Engstrom PF, Weiner LM, Cheng JD, Alpaugh RK, Cooper H, Wright JJ, et al. A phase II trial of the proteasome inhibitor bortezomib in patients with advanced biliary tract cancers. Clin Colorectal Cancer 2014; 13:81-6; PMID:24512954; http://dx.doi.org/10.1016/j.clcc.2013.12.005
327. Argiris A, Ghebremichael M, Burtness B, Axelrod RS, Deconti RC, Forastiere AA. A phase 2 trial of bortezomib followed by the addition of doxorubicin at progression in patients with recurrent or metastatic adenoid cystic carcinoma of the head and neck: a trial of the Eastern Cooperative Oncology Group (E1303). Cancer 2011; 117:3374-82; PMID:21246525; http://dx.doi.org/10.1002/cncr.25852
328. Gilbert J, Lee JW, Argiris A, Haigentz M, Jr., Feldman LE, Jang M, Arun P, Van Waes C, Forastiere AA. Phase II 2-arm trial of the proteasome inhibitor, PS-341 (bortezomib) in combination with irinotecan or PS-341 alone followed by the addition of irinotecan at time of progression in patients with locally recurrent or metastatic squamous cell carcinoma of the head and neck (E1304): a trial of the Eastern Cooperative Oncology Group. Head Neck 2013; 35:942-8; PMID:22791234; http://dx.doi.org/10.1002/hed.23046
329. Friday BB, Anderson SK, Buckner J, Yu C, Giannini C, Geoffroy F, Schwerkoske J, Mazurczak M, Gross H, Pajon E, et al. Phase II trial of vorinostat in combination with bortezomib in recurrent glioblastoma: a north central cancer treatment group study. Neuro Oncol 2012; 14:215-21; PMID:22090453; http://dx.doi.org/10.1093/neuonc/nor198
330. O'Brien ME, Gaafar RM, Popat S, Grossi F, Price A, Talbot DC, Cufer T, Ottensmeier C, Danson S, Pallis A, et al. Phase II study of first-line bortezomib and cisplatin in malignant pleural mesothelioma and prospective validation of progression free survival rate as a primary end-point for mesothelioma clinical trials (European Organisation for Research and Treatment of Cancer 08052). Eur J Cancer 2013; 49:2815-22; PMID:23791541; http://dx.doi.org/10.1016/j.ejca.2013.05.008
331. Irvin WJ, Jr., Orlowski RZ, Chiu WK, Carey LA, Collichio FA, Bernard PS, Stijleman IJ, Perou C, Ivanova A, Dees EC. Phase II study of bortezomib and pegylated liposomal doxorubicin in the treatment of metastatic breast cancer. Clin Breast Cancer 2010; 10:465-70; PMID:21147690; http://dx.doi.org/10.3816/CBC.2010.n.061
332. Hoang T, Campbell TC, Zhang C, Kim K, Kolesar JM, Oettel KR, Blank JH, Robinson EG, Ahuja HG, Kirschling RJ, et al. Vorinostat and bortezomib as third-line therapy in patients with advanced non-small cell lung cancer: a Wisconsin Oncology Network Phase II study. Invest New Drugs 2014; 32:195-9; PMID:23728919; http://dx.doi.org/10.1007/s10637-013-9980-5
333. Ciombor KK, Feng Y, Benson AB, 3rd, Su Y, Horton L, Short SP, Kauh JS, Staley C, Mulcahy M, Powell M, et al. Phase II trial of bortezomib plus doxorubicin in hepatocellular carcinoma (E6202): a trial of the Eastern Cooperative Oncology Group. Invest New Drugs 2014; PMID:24890858; http://dx.doi.org/10.1007/s10637-014-0111-8
334. Morris MJ, Kelly WK, Slovin S, Ryan C, Eicher C, Heller G, Scher HI. A phase II trial of bortezomib and prednisone for castration resistant metastatic prostate cancer. J Urol 2007; 178:2378-83; discussion 83–4; PMID:17936848; http://dx.doi.org/10.1016/j.juro.2007.08.015
335. Galluzzi L. New immunotherapeutic paradigms for castration-resistant prostate cancer. Oncoimmunology 2013; 2:e26084
336. Hainsworth JD, Meluch AA, Spigel DR, Barton J, Jr., Simons L, Meng C, Gould B, Greco FA. Weekly docetaxel and bortezomib as first-line treatment for patients with hormone-refractory prostate cancer: a Minnie Pearl Cancer Research Network phase II trial. Clin Genitourin Cancer 2007; 5:278-83; PMID:17553208;
337. Parma G, Mancari R, Del Conte G, Scambia G, Gadducci A, Hess D, Katsaros D, Sessa C, Rinaldi A, Bertoni F, et al. An open-label phase 2 study of twice-weekly bortezomib and intermittent pegylated liposomal doxorubicin in patients with ovarian cancer failing platinum-containing regimens. Int J Gynecol Cancer 2012; 22:792-800; PMID:22635029; http://dx.doi.org/10.1097/IGC.0b013e318251051a
338. Miller Z, Ao L, Kim KB, Lee W. Inhibitors of the immunoproteasome: current status and future directions. Curr Pharm Des 2013; 19:4140-51; PMID:23181576
339. Bellavista E, Andreoli F, Parenti MD, Martucci M, Santoro A, Salvioli S, Capri M, Baruzzi A, Del Rio A, Franceschi C, et al. Immunoproteasome in cancer and neuropathologies: a new therapeutic target? Curr Pharm Des 2013; 19:702-18; PMID:23016859; http://dx.doi.org/10.2174/138161213804581927
340. Huber EM, Groll M. Inhibitors for the immuno- and constitutive proteasome: current and future trends in drug development. Angew Chem Int Ed Engl 2012; 51:8708-20; PMID:22711561; http://dx.doi.org/10.1002/anie.201201616
341. Cenci S, Oliva L, Cerruti F, Milan E, Bianchi G, Raule M, Mezghrani A, Pasqualetto E, Sitia R, Cascio P. Pivotal Advance: protein synthesis modulates responsiveness of differentiating and malignant plasma cells to proteasome inhibitors. J Leukoc Biol 2012; 92:921-31; PMID:22685320; http://dx.doi.org/10.1189/jlb.1011497
342. Kisselev AF, Callard A, Goldberg AL. Importance of the different proteolytic sites of the proteasome and the efficacy of inhibitors varies with the protein substrate. J Biol Chem 2006; 281:8582-90; PMID:16455650; http://dx.doi.org/10.1074/jbc.M509043200
343. Hoffmann J, Vitale I, Buchmann B, Galluzzi L, Schwede W, Senovilla L, Skuballa W, Vivet S, Lichtner RB, Vicencio JM, et al. Improved cellular pharmacokinetics and pharmacodynamics underlie the wide anticancer activity of sagopilone. Cancer Res 2008; 68:5301-8; PMID:18593931; http://dx.doi.org/10.1158/0008-5472.CAN-08-0237
344. Domenech E, Malumbres M. Mitosis-targeting therapies: a troubleshooting guide. Curr Opin Pharmacol 2013; 13:519-28; PMID:23583638; http://dx.doi.org/10.1016/j.coph.2013.03.011
345. Jordan MA, Wilson L. Microtubules as a target for anticancer drugs. Nat Rev Cancer 2004; 4:253-65; PMID:15057285; http://dx.doi.org/10.1038/nrc1317
346. Kharaziha P, Ceder S, Sanchez C, Panaretakis T. Multitargeted therapies for multiple myeloma. Autophagy 2013; 9:255-7; PMID:23183549; http://dx.doi.org/10.4161/auto.22738
347. Kharaziha P, De Raeve H, Fristedt C, Li Q, Gruber A, Johnsson P, Kokaraki G, Panzar M, Laane E, Osterborg A, et al. Sorafenib has potent antitumor activity against multiple myeloma in vitro, ex vivo, and in vivo in the 5T33MM mouse model. Cancer Res 2012; 72:5348-62; PMID:22952216; http://dx.doi.org/10.1158/0008-5472.CAN-12-0658
348. Kharaziha P, Rodriguez P, Li Q, Rundqvist H, Bjorklund AC, Augsten M, Ullén A, Egevad L, Wiklund P, Nilsson S, et al. Targeting of distinct signaling cascades and cancer-associated fibroblasts define the efficacy of Sorafenib against prostate cancer cells. Cell Death Dis 2012; 3:e262; PMID:22278289; http://dx.doi.org/10.1038/cddis.2012.1
349. Lainey E, Wolfromm A, Marie N, Enot D, Scoazec M, Bouteloup C, Leroy C, Micol JB, De Botton S, Galluzzi L, et al. Azacytidine and erlotinib exert synergistic effects against acute myeloid leukemia. Oncogene 2013; 32:4331-42; PMID:23085751; http://dx.doi.org/10.1038/onc.2012.469
350. Kepp O, Galluzzi L, Kroemer G. Immune effectors required for the therapeutic activity of vorinostat. Oncoimmunology 2013; 2:e27157; PMID:24475375
351. Galluzzi L, Vitale I, Senovilla L, Olaussen KA, Pinna G, Eisenberg T, Goubar A, Martins I, Michels J, Kratassiouk G, et al. Prognostic impact of vitamin B6 metabolism in lung cancer. Cell Rep 2012; 2:257-69; PMID:22854025; http://dx.doi.org/10.1016/j.celrep.2012.06.017
352. Galluzzi L, Senovilla L, Vitale I, Michels J, Martins I, Kepp O, Castedo M, Kroemer G. Molecular mechanisms of cisplatin resistance. Oncogene 2012; 31:1869-83; PMID:21892204; http://dx.doi.org/10.1038/onc.2011.384
353. Tajeddine N, Galluzzi L, Kepp O, Hangen E, Morselli E, Senovilla L, Araujo N, Pinna G, Larochette N, Zamzami N, et al. Hierarchical involvement of Bak, VDAC1 and Bax in cisplatin-induced cell death. Oncogene 2008; 27:4221-32; PMID:18362892; http://dx.doi.org/10.1038/onc.2008.63
354. Cirone M, Garufi A, Di Renzo L, Granato M, Faggioni A, D'Orazi G. Zinc supplementation is required for the cytotoxic and immunogenic effects of chemotherapy in chemoresistant p53-functionally deficient cells. Oncoimmunology 2013; 2:e26198; PMID:24228232
355. Balfour JA, McClellan K. Topical eflornithine. Am J Clin Dermatol 2001; 2:197-201; discussion 2; PMID:11705097; http://dx.doi.org/10.2165/00128071-200102030-00009
356. Rounbehler RJ, Li W, Hall MA, Yang C, Fallahi M, Cleveland JL. Targeting ornithine decarboxylase impairs development of MYCN-amplified neuroblastoma. Cancer Res 2009; 69:547-53; PMID:19147568; http://dx.doi.org/10.1158/0008-5472.CAN-08-2968
357. Pegg AE. Polyamine metabolism and its importance in neoplastic growth and a target for chemotherapy. Cancer Res 1988; 48:759-74
358. Burri C, Brun R. Eflornithine for the treatment of human African trypanosomiasis. Parasitol Res 2003; 90 Supp 1:S49-52
359. Elion GB. Acyclovir: discovery, mechanism of action, and selectivity. J Med Virol 1993; Suppl 1:2-6; PMID:8245887; http://dx.doi.org/10.1002/jmv.1890410503
360. McMahon MA, Siliciano JD, Lai J, Liu JO, Stivers JT, Siliciano RF, Kohli RM. The antiherpetic drug acyclovir inhibits HIV replication and selects the

V75I reverse transcriptase multidrug resistance mutation. J Biol Chem 2008; 283:31289-93; PMID:18818198; http://dx.doi.org/10.1074/jbc.C800188200
361. Lisco A, Vanpouille C, Tchesnokov EP, Grivel JC, Biancotto A, Brichacek B, Lambotte O, Meyer L, Gougeon ML, Zitvogel L. Acyclovir is activated into a HIV-1 reverse transcriptase inhibitor in herpesvirus-infected human tissues. Cell Host Microbe 2008; 4:260-70; PMID:18779052; http://dx.doi.org/10.1016/j.chom.2008.07.008
362. Prada N, Antoni G, Commo F, Rusakiewicz S, Semeraro M, Boufassa F, Lambotte O, Meyer L, Gougeon ML, Zitvogel L. Analysis of NKp30/NCR3 isoforms in untreated HIV-1-infected patients from the ANRS SEROCO cohort. Oncoimmunology 2013; 2: e23472; PMID:23802087
363. Buac D, Shen M, Schmitt S, Kona FR, Deshmukh R, Zhang Z, Neslund-Dudas C, Mitra B, Dou QP. From bortezomib to other inhibitors of the proteasome and beyond. Curr Pharm Des 2013; 19:4025-38; PMID:23181572; http://dx.doi.org/10.2174/1381612811319220012
364. Cao B, Li J, Mao X. Dissecting bortezomib: development, application, adverse effects and future direction. Curr Pharm Des 2013; 19:3190-200; PMID:23151134; http://dx.doi.org/10.2174/13816128113199990338
365. Ruschak AM, Slassi M, Kay LE, Schimmer AD. Novel proteasome inhibitors to overcome bortezomib resistance. J Natl Cancer Inst 2011; 103:1007-17; PMID:21606441; http://dx.doi.org/10.1093/jnci/djr160
366. Shaughnessy JD, Jr., Qu P, Usmani S, Heuck CJ, Zhang Q, Zhou Y, Tian E, Hanamura I, van Rhee F, Anaissie E, et al. Pharmacogenomics of bortezomib test-dosing identifies hyperexpression of proteasome genes, especially PSMD4, as novel high-risk feature in myeloma treated with Total Therapy 3. Blood 2011; 118:3512-24; PMID:21628408; http://dx.doi.org/10.1182/blood-2010-12-328252
367. Oerlemans R, Franke NE, Assaraf YG, Cloos J, van Zantwijk I, Berkers CR, Scheffer GL, Debipersad K, Vojtekova K, Lemos C, et al. Molecular basis of bortezomib resistance: proteasome subunit beta5 (PSMB5) gene mutation and overexpression of PSMB5 protein. Blood 2008; 112:2489-99; PMID:18565852; http://dx.doi.org/10.1182/blood-2007-08-104950
368. Lu S, Chen Z, Yang J, Chen L, Gong S, Zhou H, Guo L, Wang J. Overexpression of the PSMB5 gene contributes to bortezomib resistance in T-lymphoblastic lymphoma/leukemia cells derived from Jurkat line. Exp Hematol 2008; 36:1278-84; PMID:18562081; http://dx.doi.org/10.1016/j.exphem.2008.04.013
369. Franke NE, Niewerth D, Assaraf YG, van Meerloo J, Vojtekova K, van Zantwijk CH, Zweegman S, Chan ET, Kirk CJ, Geerke DP, et al. Impaired bortezomib binding to mutant beta5 subunit of the proteasome is the underlying basis for bortezomib resistance in leukemia cells. Leukemia 2012; 26:757-68; PMID:21941364; http://dx.doi.org/10.1038/leu.2011.256
370. Lu S, Yang J, Chen Z, Gong S, Zhou H, Xu X, Wang J. Different mutants of PSMB5 confer varying bortezomib resistance in T lymphoblastic lymphoma/leukemia cells derived from the Jurkat cell line. Exp Hematol 2009; 37:831-7; PMID:19426847; http://dx.doi.org/10.1016/j.exphem.2009.04.001
371. Markovina S, Callander NS, O'Connor SL, Kim J, Werndli JE, Raschko M, Leith CP, Kahl BS, Kim K, Miyamoto S. Bortezomib-resistant nuclear factor-kappaB activity in multiple myeloma cells. Mol Cancer Res 2008; 6:1356-64; PMID:18708367; http://dx.doi.org/10.1158/1541-7786.MCR-08-0108
372. Yang DT, Young KH, Kahl BS, Markovina S, Miyamoto S. Prevalence of bortezomib-resistant constitutive NF-kappaB activity in mantle cell lymphoma. Mol Cancer 2008; 7:40; PMID:18489772; http://dx.doi.org/10.1186/1476-4598-7-40
373. Kuhn DJ, Berkova Z, Jones RJ, Woessner R, Bjorklund CC, Ma W, Davis RE, Lin P, Wang H, Madden TL, et al. Targeting the insulin-like growth factor-1 receptor to overcome bortezomib resistance in preclinical models of multiple myeloma. Blood 2012; 120:3260-70; PMID:22932796; http://dx.doi.org/10.1182/blood-2011-10-386789
374. Feng Y, Dimitrov DS. Antibody-based therapeutics against components of the IGF system. Oncoimmunology 2012; 1:1390-1; PMID:23243603; http://dx.doi.org/10.4161/onci.20925
375. Busacca S, Chacko AD, Klabatsa A, Arthur K, Sheaff M, Gunasekharan VK, Gorski JJ, El-Tanani M, Broaddus VC, Gaudino G, et al. BAK and NOXA are critical determinants of mitochondrial apoptosis induced by bortezomib in mesothelioma. PLoS One 2013; 8:e65489; PMID:23762382; http://dx.doi.org/10.1371/journal.pone.0065489
376. Kern J, Untergasser G, Zenzmaier C, Sarg B, Gastl G, Gunsilius E, Steurer M. GRP-78 secreted by tumor cells blocks the antiangiogenic activity of bortezomib. Blood 2009; 114:3960-7; PMID:19713465; http://dx.doi.org/10.1182/blood-2009-03-209668
377. Gutman D, Morales AA, Boise LH. Acquisition of a multidrug-resistant phenotype with a proteasome inhibitor in multiple myeloma. Leukemia 2009; 23:2181-3; PMID:19516276; http://dx.doi.org/10.1038/leu.2009.123
378. Lainey E, Sebert M, Thepot S, Scoazec M, Bouteloup C, Leroy C, De Botton S, Galluzzi L, Fenaux P, Kroemer G. Erlotinib antagonizes ABC transporters in acute myeloid leukemia. Cell Cycle 2012; 11:4079-92; PMID:23095522; http://dx.doi.org/10.4161/cc.22382
379. Riganti C, Massaia M. Inhibition of the mevalonate pathway to override chemoresistance and promote the immunogenic demise of cancer cells: killing two birds with one stone. Oncoimmunology 2013; 2:e25770
380. Weniger MA, Rizzatti EG, Perez-Galan P, Liu D, Wang Q, Munson PJ, Raghavachari N, White T, Tweito MM, Dunleavy K, et al. Treatment-induced oxidative stress and cellular antioxidant capacity determine response to bortezomib in mantle cell lymphoma. Clin Cancer Res 2011; 17:5101-12; PMID:21712452; http://dx.doi.org/10.1158/1078-0432.CCR-10-3367
381. Parlati F, Lee SJ, Aujay M, Suzuki E, Levitsky K, Lorens JB, Micklem DR, Ruurs P, Sylvain C, Lu Y, et al. Carfilzomib can induce tumor cell death through selective inhibition of the chymotrypsin-like activity of the proteasome. Blood 2009; 114:3439-47; PMID:19671918; http://dx.doi.org/10.1182/blood-2009-05-223677
382. Demo SD, Kirk CJ, Aujay MA, Buchholz TJ, Dajee M, Ho MN, Jiang J, Laidig GJ, Lewis ER, Parlati F, et al. Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. Cancer Res 2007; 67:6383-91; PMID:17616698; http://dx.doi.org/10.1158/0008-5472.CAN-06-4086
383. Kuhn DJ, Chen Q, Voorhees PM, Strader JS, Shenk KD, Sun CM, Demo SD, Bennett MK, van Leeuwen FW, Chanan-Khan AA, et al. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. Blood 2007; 110:3281-90; PMID:17591945; http://dx.doi.org/10.1182/blood-2007-01-065888
384. Alsina M, Trudel S, Furman RR, Rosen PJ, O'Connor OA, Comenzo RL, Wong A, Kunkel LA, Molineaux CJ, Goy A. A phase I single-agent study of twice-weekly consecutive-day dosing of the proteasome inhibitor carfilzomib in patients with relapsed or refractory multiple myeloma or lymphoma. Clin Cancer Res 2012; 18:4830-40; PMID:22761464;
385. O'Connor OA, Stewart AK, Vallone M, Molineaux CJ, Kunkel LA, Gerecitano JF, Orlowski RZ. A phase 1 dose escalation study of the safety and pharmacokinetics of the novel proteasome inhibitor carfilzomib (PR-171) in patients with hematologic malignancies. Clin Cancer Res 2009; 15:7085-91; PMID:19903785; http://dx.doi.org/10.1158/1078-0432.CCR-09-0822
386. Kortuem KM, Stewart AK. Carfilzomib. Blood 2013; 121:893-7; PMID:23393020; http://dx.doi.org/10.1182/blood-2012-10-459883
387. Jakubowiak AJ, Siegel DS, Martin T, Wang M, Vij R, Lonial S, Trudel S, Kukreti V, Bahlis N, Alsina M, et al. Treatment outcomes in patients with relapsed and refractory multiple myeloma and high-risk cytogenetics receiving single-agent carfilzomib in the PX-171-003-A1 study. Leukemia 2013; 27:2351-6; PMID:23670297; http://dx.doi.org/10.1038/leu.2013.152
388. Siegel D, Martin T, Nooka A, Harvey RD, Vij R, Niesvizky R, Badros AZ, Jagannath S, McCulloch L, Rajangam K, et al. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. Haematologica 2013; 98:1753-61; PMID:23935022; http://dx.doi.org/10.3324/haematol.2013.089334
389. Niesvizky R, Martin TG, 3rd, Bensinger WI, Alsina M, Siegel DS, Kunkel LA, Wong AF, Lee S, Orlowski RZ, Wang M. Phase Ib dose-escalation study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma. Clin Cancer Res 2013; 19:2248-56; PMID:23447001; http://dx.doi.org/10.1158/1078-0432.CCR-12-3352
390. Wang M, Martin T, Bensinger W, Alsina M, Siegel DS, Kavalerchik E, Huang M, Orlowski RZ, Niesvizky R. Phase 2 dose-expansion study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma. Blood 2013; 122:3122-8; PMID:24014245; http://dx.doi.org/10.1182/blood-2013-07-511170
391. Jakubowiak AJ, Dytfeld D, Griffith KA, Lebovic D, Vesole DH, Jagannath S, Al-Zoubi A, Anderson T, Nordgren B, Detweiler-Short K, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood 2012; 120:1801-9; PMID:22665938; http://dx.doi.org/10.1182/blood-2012-04-422683
392. Berenson JR, Hilger JD, Yellin O, Dichmann R, Patel-Donnelly D, Boccia RV, Bessudo A, Stampleman L, Gravenor D, Eshaghian S, et al. Replacement of bortezomib with carfilzomib for multiple myeloma patients progressing from bortezomib combination therapy. Leukemia 2014; 28:1529-36; PMID:24429497; http://dx.doi.org/10.1038/leu.2014.27
393. Bringhen S, Petrucci MT, Larocca A, Conticello C, Rossi D, Magarotto V, Musto P, Boccadifuoco L, Offidani M, Omedé P, et al. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. Blood 2014; 124:63-9; PMID:24855212; http://dx.doi.org/10.1182/blood-2014-03-563759
394. Hajek R, Bryce R, Ro S, Klencke B, Ludwig H. Design and rationale of FOCUS (PX-171-011): a randomized, open-label, phase 3 study of carfilzomib versus best supportive care regimen in patients with relapsed and refractory multiple myeloma (R/R MM). BMC Cancer 2012; 12:415; PMID:22992303; http://dx.doi.org/10.1186/1471-2407-12-415
395. Papadopoulos KP, Burris HA, 3rd, Gordon M, Lee P, Sausville EA, Rosen PJ, Patnaik A, Cutler RE Jr, Wang Z, Lee S, et al. A phase I/II study of carfilzomib 2-10-min infusion in patients with advanced solid tumors. Cancer Chemother Pharmacol 2013; 72: 861-8; PMID:23975329; http://dx.doi.org/10.1007/s00280-013-2267-x
396. West AC, Smyth MJ, Johnstone RW. The anticancer effects of HDAC inhibitors require the immune

system. Oncoimmunology 2014; 3:e27414; PMID:24701376
397. Prince HM, Bishton MJ, Harrison SJ. Clinical studies of histone deacetylase inhibitors. Clin Cancer Res 2009; 15:3958-69; PMID:19509172; http://dx.doi.org/10.1158/1078-0432.CCR-08-2785
398. West AC, Johnstone RW. New and emerging HDAC inhibitors for cancer treatment. J Clin Invest 2014; 124:30-9; PMID:24382387; http://dx.doi.org/10.1172/JCI69738
399. McGraw AL. Romidepsin for the treatment of T-cell lymphomas. Am J Health Syst Pharm 2013; 70: 1115-22
400. Piekarz RL, Frye R, Turner M, Wright JJ, Allen SL, Kirschbaum MH, Zain J, Prince HM, Leonard JP, Geskin LJ, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol 2009; 27:5410-7; PMID:19826128; http://dx.doi.org/10.1200/JCO.2008.21.6150
401. Weiss RB, Christian MC. New cisplatin analogues in development. A review. Drugs 1993; 46:360-77; PMID:7693428; http://dx.doi.org/10.2165/00003495-199346030-00003
402. Harrap KR. Preclinical studies identifying carboplatin as a viable cisplatin alternative. Cancer Treat Rev 1985; 12 Suppl A:21-33
403. Vonderheide RH, Burg JM, Mick R, Trosko JA, Li D, Shaik MN, Tolcher AW, Hamid O. Phase I study of the CD40 agonist antibody CP-870,893 combined with carboplatin and paclitaxel in patients with advanced solid tumors. Oncoimmunology 2013; 2: e23033; PMID:23483678
404. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 2000; 343:905-14; PMID:11006366; http://dx.doi.org/10.1056/NEJM200009283431302
405. Kawato Y, Aonuma M, Hirota Y, Kuga H, Sato K. Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. Cancer Res 1991; 51:4187-91; PMID:1651156
406. Obaidat A, Weiss J, Wahlgren B, Manam RR, Macherla VR, McArthur K, Chao TH, Palladino MA, Lloyd GK, Potts BC, et al. Proteasome regulator marizomib (NPI-0052) exhibits prolonged inhibition, attenuated efflux, and greater cytotoxicity than its reversible analogs. J Pharmacol Exp Ther 2011; 337:479-86; PMID:21303921; http://dx.doi.org/10.1124/jpet.110.177824
407. Potts BC, Albitar MX, Anderson KC, Baritaki S, Berkers C, Bonavida B, Chandra J, Chauhan D, Cusack JC Jr, Fenical W, et al. Marizomib, a proteasome inhibitor for all seasons: preclinical profile and a framework for clinical trials. Curr Cancer Drug Targets 2011; 11:254-84; PMID:21247382; http://dx.doi.org/10.2174/156800911794519716
408. Chauhan D, Hideshima T, Anderson KC. A novel proteasome inhibitor NPI-0052 as an anticancer therapy. Br J Cancer 2006; 95:961-5; PMID:17047643; http://dx.doi.org/10.1038/sj.bjc.6603406
409. Chauhan D, Catley L, Li G, Podar K, Hideshima T, Velankar M, Mitsiades C, Mitsiades N, Yasui H, Letai A, et al. A novel orally active proteasome inhibitor induces apoptosis in multiple myeloma cells with mechanisms distinct from Bortezomib. Cancer Cell 2005; 8:407-19; PMID:16286248; http://dx.doi.org/10.1016/j.ccr.2005.10.013
410. Feling RH, Buchanan GO, Mincer TJ, Kauffman CA, Jensen PR, Fenical W. Salinosporamide A: a highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus salinospora. Angew Chem Int Ed Engl 2003; 42:355-7; PMID:12548698; http://dx.doi.org/10.1002/anie.200390115
411. Allegra A, Alonci A, Gerace D, Russo S, Innao V, Calabro L, Musolino C. New orally active proteasome inhibitors in multiple myeloma. Leuk Res 2014; 38:1-9; PMID:24239172; http://dx.doi.org/10.1016/j.leukres.2013.10.018
412. Singh AV, Palladino MA, Lloyd GK, Potts BC, Chauhan D, Anderson KC. Pharmacodynamic and efficacy studies of the novel proteasome inhibitor NPI-0052 (marizomib) in a human plasmacytoma xenograft murine model. Br J Haematol 2010; 149:550-9; PMID:20331453; http://dx.doi.org/10.1111/j.1365-2141.2010.08144.x
413. Miller CP, Rudra S, Keating MJ, Wierda WG, Palladino M, Chandra J. Caspase-8 dependent histone acetylation by a novel proteasome inhibitor, NPI-0052: a mechanism for synergy in leukemia cells. Blood 2009; 113:4289-99; PMID:19182209; http://dx.doi.org/10.1182/blood-2008-08-174797
414. Cusack JC, Jr., Liu R, Xia L, Chao TH, Pien C, Niu W, Palombella VJ, Neuteboom ST, Palladino MA. NPI-0052 enhances tumoricidal response to conventional cancer therapy in a colon cancer model. Clin Cancer Res 2006; 12:6758-64; PMID:17121896; http://dx.doi.org/10.1158/1078-0432.CCR-06-1151
415. Ruiz S, Krupnik Y, Keating M, Chandra J, Palladino M, McConkey D. The proteasome inhibitor NPI-0052 is a more effective inducer of apoptosis than bortezomib in lymphocytes from patients with chronic lymphocytic leukemia. Mol Cancer Ther 2006; 5:1836-43; PMID:16891470; http://dx.doi.org/10.1158/1535-7163.MCT-06-0066
416. Kupperman E, Lee EC, Cao Y, Bannerman B, Fitzgerald M, Berger A, Yu J, Yang Y, Hales P, Bruzzese F, et al. Evaluation of the proteasome inhibitor MLN9708 in preclinical models of human cancer. Cancer Res 2010; 70:1970-80; PMID:20160034; http://dx.doi.org/10.1158/0008-5472.CAN-09-2766
417. Roccaro AM, Sacco A, Aujay M, Ngo HT, Azab AK, Azab F, Quang P, Maiso P, Runnels J, Anderson KC, Gillenwater HH, Infante JR. Selective inhibition of chymotrypsin-like activity of the immunoproteasome and constitutive proteasome in Waldenstrom macroglobulinemia. Blood 2010; 115:4051-60; PMID:20110419; http://dx.doi.org/10.1182/blood-2009-09-243402
418. Zhou HJ, Aujay MA, Bennett MK, Dajee M, Demo SD, Fang Y, Ho MN, Jiang J, Kirk CJ, Laidig GJ, et al. Design and synthesis of an orally bioavailable and selective peptide epoxyketone proteasome inhibitor (PR-047). J Med Chem 2009; 52:3028-38; PMID:19348473; http://dx.doi.org/10.1021/jm801329v
419. Zang Y, Thomas SM, Chan ET, Kirk CJ, Freilino ML, DeLancey HM, Grandis JR, Li C, Johnson DE. Carfilzomib and ONX 0912 inhibit cell survival and tumor growth of head and neck cancer and their activities are enhanced by suppression of Mcl^{-}1 or autophagy. Clin Cancer Res 2012; 18:5639-49; PMID:22929803; http://dx.doi.org/10.1158/1078-0432.CCR-12-1213
420. Chauhan D, Singh AV, Aujay M, Kirk CJ, Bandi M, Ciccarelli B, Raje N, Richardson P, Anderson KC. A novel orally active proteasome inhibitor ONX 0912 triggers in vitro and in vivo cytotoxicity in multiple myeloma. Blood 2010; 116:4906-15; PMID:20805366; http://dx.doi.org/10.1182/blood-2010-04-276626
421. Sala F, Marangon E, Bagnati R, Livi V, Cereda R, D'Incalci M, Zucchetti M. Development and validation of a high-performance liquid chromatography-tandem mass spectrometry method for the determination of the novel proteasome inhibitor CEP-18770 in human plasma and its application in a clinical pharmacokinetic study. J Mass Spectrom 2010; 45:1299-305; PMID:20872901; http://dx.doi.org/10.1002/jms.1842
422. Dorsey BD, Iqbal M, Chatterjee S, Menta E, Bernardini R, Bernareggi A, Cassarà PG, D'Arasmo G, Ferretti E, De Munari S, et al. Discovery of a potent, selective, and orally active proteasome inhibitor for the treatment of cancer. J Med Chem 2008; 51:1068-72; PMID:18247547; http://dx.doi.org/10.1021/jm7010589
423. Berkers CR, Leestemaker Y, Schuurman KG, Ruggeri B, Jones-Bolin S, Williams M, Ovaa H. Probing the specificity and activity profiles of the proteasome inhibitors bortezomib and delanzomib. Mol Pharm 2012; 9:1126-35; PMID:22432738; http://dx.doi.org/10.1021/mp2004143
424. Piva R, Ruggeri B, Williams M, Costa G, Tamagno I, Ferrero D, Giai V, Coscia M, Peola S, Massaia M, et al. CEP-18770: a novel, orally active proteasome inhibitor with a tumor-selective pharmacologic profile competitive with bortezomib. Blood 2008; 111:2765-75; PMID:18057228; http://dx.doi.org/10.1182/blood-2007-07-100651
425. Sanchez E, Li M, Steinberg JA, Wang C, Shen J, Bonavida B, Li ZW, Chen H, Berenson JR. The proteasome inhibitor CEP-18770 enhances the anti-myeloma activity of bortezomib and melphalan. Br J Haematol 2010; 148:569-81; PMID:19958357; http://dx.doi.org/10.1111/j.1365-2141.2009.08008.x
426. Sanchez E, Li M, Li J, Wang C, Chen H, Jones-Bolin S, Hunter K, Ruggeri B, Berenson JR. CEP-18770 (delanzomib) in combination with dexamethasone and lenalidomide inhibits the growth of multiple myeloma. Leuk Res 2012; 36:1422-7; PMID:22906694; http://dx.doi.org/10.1016/j.leukres.2012.07.018
427. Chauhan D, Singh A, Brahmandam M, Podar K, Hideshima T, Richardson P, Munshi N, Palladino MA, Anderson KC. Combination of proteasome inhibitors bortezomib and NPI-0052 trigger in vivo synergistic cytotoxicity in multiple myeloma. Blood 2008; 111:1654-64; PMID:18006697; http://dx.doi.org/10.1182/blood-2007-08-105601
428. Richardson PG, Spencer A, Cannell P, Harrison SJ, Catley L, Underhill C, Zimmerman TM, Hofmeister CC, Jakubowiak AJ, Laubach JP, Palladino MA, Longenecker AM, Lay A, Wear S, Lloyd GK, Hannah AL, Reich S, Spear MA, Anderson KC. Phase 1 clinical evaluation of twice-weekly marizomib (NPI-0052), a novel proteasome inhibitor, in patients with relapsed/refractory multiple myeloma (MM). Blood 2011; 118:abstr 302.
429. Millward M, Price T, Townsend A, Sweeney C, Spencer A, Sukumaran S, Longenecker A, Lee L, Lay A, Sharma G, et al. Phase 1 clinical trial of the novel proteasome inhibitor marizomib with the histone deacetylase inhibitor vorinostat in patients with melanoma, pancreatic and lung cancer based on in vitro assessments of the combination. Invest New Drugs 2012; 30:2303-17; PMID:22080430; http://dx.doi.org/10.1007/s10637-011-9766-6
430. Richardson PG, Siegel DS, Vij R, Hofmeister CC, Baz R, Jagannath S, Chen C, Lonial S, Jakubowiak A, Bahlis N, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood 2014; 123:1826-32; PMID:24421329; http://dx.doi.org/10.1182/blood-2013-11-538835
431. Traynor K. Pomalidomide approved for multiple myeloma. Am J Health Syst Pharm 2013; 70:474
432. Leleu X, Attal M, Arnulf B, Moreau P, Traulle C, Marit G, Mathiot C, Petillon MO, Macro M, Roussel M, et al. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: intergroupe Francophone du Myelome 2009-02. Blood 2013; 121:1968-75; PMID:23319574; http://dx.doi.org/10.1182/blood-2012-09-452375
433. Richardson PG, Siegel D, Baz R, Kelley SL, Munshi NC, Laubach J, Sullivan D, Alsina M, Schlossman R, Ghobrial IM, et al. Phase 1 study of pomalidomide MTD, safety, and efficacy in patients with refractory multiple myeloma who have received lenalidomide and bortezomib. Blood 2013; 121:1961-7; PMID:23243282; http://dx.doi.org/10.1182/blood-2012-08-450742

434. Kumar SK, Bensinger WI, Zimmerman TM, Reeder CB, Berenson JR, Berg D, et al. Weekly dosing of the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma: results from a phase 1 study. Blood 2014 Aug 14;124(7):1047-55. Epub 2014 Jun 5.; http://dx.doi.org/10.1182/blood-2014-01-548941
435. Richardson PG, Baz R, Wang M, Jakubowiak AJ, Laubach JP, Harvey RD, et al. Phase 1 study of twice-weekly dosing of investigational oral proteasome inhibitor ixazomib in patients with relapsed and/or refractory multiple myeloma. Blood 2014 Aug 14;124 (7):1038-46. Epub 2014 Jun 11; http://dx.doi.org/10.1182/blood-2014-01-548826
436. Richardson PG, Baz R, Wang L, Jakubowiak AJ, Berg D, Liu F, Gupta N, Di Bacco A, Hui AM, Lonia, S. Investigational agent MLN9708, an oral proteasome inhibitor, in patients (Pts) with relapsed and/or refractory multiple myeloma (MM): results from the expansion cohorts of a Phase 1 dose-escalation study. Blood 2011; 118:abstr 301.
437. Gupta N, Saleh M, Venkatakrishnan K. Flat-dosing versus BSA-based dosing for MLN9708, an investigational proteasome inhibitor: population pharmacokinetic (PK) analysis of pooled data from 4 Phase 1 studies. Blood 2011; 118:abstr 1433.
438. Assouline S, Chang JE, Cheson BD, Rifkin R, Hamburg S, Reyes R, Hui AM, Yu J, Gupta N, Di Bacco A, Shou Y, Martin P. Results of a Phase 1 dose-escalation study of once-weekly MLN9708, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma. Blood 2012; 120:abstr 3646.
439. Lonial S, Baz RC, Wang M, Talpaz M, Liu G, Berg D, Gupta N, Di Bacco A, Hui AM, Richardson PG. Phase I study of twice-weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM). J Clin Oncol 2012; 30:abstr 8017.
440. Martin P, Chang JE, Rifkin RM, Hui AM, Berg D, Gupta N, Liu G, Di Bacco A, Assouline SE. MLN9708, an investigational proteasome inhibitor, in patients (pts) with relapsed/refractory lymphoma: emerging data from a phase I dose-escalation study. J Clin Oncol 2012; 30:abstr 8064.
441. Berdeja JG, Richardson PG, Lonial S, Niesvizky R, Hui AM, Berg D, Gupta N, Liu G, Di Bacco A, Kumar S. Phase 1/2 study of oral MLN9708, a novel, investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma (MM). Blood 2011; 118:abstr 479.
442. Kumar SK, Berdeja JG, Niesvizky R, Lonial S, Hamadani M, Stewart AK, Roy V, Hari P, Vescio R, Berg D, Lin JH, Di Bacco A, Gupta N, Hui AM, Richardson PG. A Phase 1/2 study of weekly MLN9708, an investigational oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma (MM). Blood 2012; 120:abstr 332.
443. Kepp O, Galluzzi L, Martins I, Schlemmer F, Adjemian S, Michaud M, Sukkurwala AQ, Menger L, Zitvogel L, Kroemer G. Molecular determinants of immunogenic cell death elicited by anticancer chemotherapy. Cancer Metastasis Rev 2011; 30:61-9; PMID:21249425; http://dx.doi.org/10.1007/s10555-011-9273-4
444. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376:1147-54; PMID:20888992; http://dx.doi.org/10.1016/S0140-6736(10)61389-X
445. Fox ME, Smith PJ. Long-term inhibition of DNA synthesis and the persistence of trapped topoisomerase II complexes in determining the toxicity of the antitumor DNA intercalators mAMSA and mitoxantrone. Cancer Res 1990; 50:5813-8; PMID:2168281
446. Sukkurwala AQ, Adjemian S, Senovilla L, Michaud M, Spaggiari S, Vacchelli E, Baracco EE, Galluzzi L, Zitvogel L, Kepp O, et al. Screening of novel immunogenic cell death inducers within the NCI Mechanistic Diversity Set. Oncoimmunology 2014; 3:e28473; PMID:25050214
447. Papadopoulos KP, Mendelson DS, Tolcher AW, Burris HA, Gordon MS, Bomba D, Gillenwater HH, Infante JR. Tolerability of split-dose oprozomib (ONX 0912) in patients with advanced refractory or recurrent solid tumors. J Clin Oncol 2012; 30:abstr e13077.
448. Savona MR, Berdeja JG, Lee SJ, Wong H, Lee JR, Gillenwater HH, Siegel DS. A Phase 1b dose-escalation study of split-dose oprozomib (ONX0912) in patients with hematologic malignancies. Blood 2012; 120:abstr 203.
449. Gallerani E, Zucchetti M, Brunelli D, Marangon E, Noberasco C, Hess D, Delmonte A, Martinelli G, Böhm S, Driessen C, et al. A first in human phase I study of the proteasome inhibitor CEP-18770 in patients with advanced solid tumours and multiple myeloma. Eur J Cancer 2013; 49:290-6; PMID:23058787; http://dx.doi.org/10.1016/j.ejca.2012.09.009
450. Ocio EM, Mateos MV, San-Miguel JF. Novel agents derived from the currently approved treatments for MM: novel proteasome inhibitors and novel IMIDs. Expert Opin Investig Drugs 2012; 21:1075-87; PMID:22621161; http://dx.doi.org/10.1517/13543784.2012.691164
451. Ale A, Bruna J, Navarro X, Udina E. Neurotoxicity induced by antineoplastic proteasome inhibitors. Neurotoxicology 2014; PMID:24525285; http://dx.doi.org/10.1016/j.neuro.2014.02.001
452. Appel A. Drugs: more shots on target. Nature 2011; 480:S40-2; PMID:22169800; http://dx.doi.org/10.1038/480S40a
453. Velasco R, Petit J, Clapes V, Verdu E, Navarro X, Bruna J. Neurological monitoring reduces the incidence of bortezomib-induced peripheral neuropathy in multiple myeloma patients. J Peripher Nerv Syst 2010; 15:17-25; PMID:20433602; http://dx.doi.org/10.1111/j.1529-8027.2010.00248.x
454. Corso A, Mangiacavalli S, Varettoni M, Pascutto C, Zappasodi P, Lazzarino M. Bortezomib-induced peripheral neuropathy in multiple myeloma: a comparison between previously treated and untreated patients. Leuk Res 2010; 34:471-4; PMID:19674790; http://dx.doi.org/10.1016/j.leukres.2009.07.022
455. Baldo BA. Adverse events to monoclonal antibodies used for cancer therapy: focus on hypersensitivity responses. Oncoimmunology 2013; 2:e26333; PMID:24251081
456. Demers M, Wagner DD. Targeting platelet function to improve drug delivery. Oncoimmunology 2012; 1:100-2; PMID:22720224; http://dx.doi.org/10.4161/onci.1.1.17962
457. Richardson PG, Sonneveld P, Schuster MW, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, et al. Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: impact of a dose-modification guideline. Br J Haematol 2009; 144:895-903; PMID:19170677; http://dx.doi.org/10.1111/j.1365-2141.2008.07573.x
458. Freimann H, Calderoni A, Cornu P, Olie R. Daily practice use of Bortezomib in relapsed/refractory multiple myeloma. Safety/efficacy results of a compassionate use program in Switzerland. Swiss Med Wkly 2007; 137:317-22; PMID:17629810
459. Orlowski RZ. Why proteasome inhibitors cannot ERADicate multiple myeloma. Cancer Cell 2013; 24:275-7; PMID:24029222; http://dx.doi.org/10.1016/j.ccr.2013.08.014
460. Ogi C, Aruga A. Immunological monitoring of anticancer vaccines in clinical trials. Oncoimmunology 2013; 2:e26012; PMID:24083085
461. Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, Rekhtman G, Masliak Z, Robak T, Shubina A, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol 2011; 12:431-40; PMID:21507715; http://dx.doi.org/10.1016/S1470-2045(11)70081-X
462. Weathington NM, Mallampalli RK. Emerging therapies targeting the ubiquitin proteasome system in cancer. J Clin Invest 2014; 124:6-12; PMID:24382383; http://dx.doi.org/10.1172/JCI71602
463. Zhang W, Sidhu SS. Development of inhibitors in the ubiquitination cascade. FEBS Lett 2014; 588:356-67; PMID:24239534; http://dx.doi.org/10.1016/j.febslet.2013.11.003
464. Schmidt M, Finley D. Regulation of proteasome activity in health and disease. Biochim Biophys Acta 2014; 1843:13-25; PMID:23994620; http://dx.doi.org/10.1016/j.bbamcr.2013.08.012
465. Sijts EJ, Kloetzel PM. The role of the proteasome in the generation of MHC class I ligands and immune responses. Cell Mol Life Sci 2011; 68:1491-502; PMID:21387144; http://dx.doi.org/10.1007/s00018-011-0657-y
466. Warnatsch A, Bergann T, Kruger E. Oxidation matters: the ubiquitin proteasome system connects innate immune mechanisms with MHC class I antigen presentation. Mol Immunol 2013; 55:106-9; PMID:23140834; http://dx.doi.org/10.1016/j.molimm.2012.10.007
467. Bossi G, Gerry AB, Paston SJ, Sutton DH, Hassan NJ, Jakobsen BK. Examining the presentation of tumor-associated antigens on peptide-pulsed T2 cells. Oncoimmunology 2013; 2:e26840; PMID:24482751
468. Chang S, Lin X, Higashikubo R, Toth K, Gelman AE, Kreisel D, Krupnick AS. Unique pulmonary antigen presentation may call for an alternative approach toward lung cancer immunotherapy. Oncoimmunology 2013; 2:e23563; PMID:23802088; http://dx.doi.org/10.4161/onci.23563