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Carfilzomib (Kyprolis) [Medicare]

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

Number: 0845m

Commercial CPB (0845.html) | Medicare CPB

Medicare Part B Step Therapy Criteria

Darzalex, **Darzalex Faspro**, and **Kyprolis**, for the indications listed below:

- Treatment of adult patients with multiple myeloma

  Are not covered for new starts, unless the member meets ANY of the following:

  1. Inadequate response to a trial of bortezomib or Velcade
  2. Intolerable adverse event to bortezomib or Velcade
  3. Bortezomib or Velcade is contraindicated for the member.

Policy

I. **Criteria for Initial Approval**

Policy History

Effective: 01/01/2022

Next Review: 12/08/2022

Definitions

Additional Information

Clinical Policy Bulletin Notes

Aetna considers carfilzomib injection (Kyprolis) medically necessary for the following indications:

A. *Multiple Myeloma*

For treatment of multiple myeloma when the requested medication will be used in *any* of the following regimens:

1. In combination with dexamethasone for relapsed or progressive disease; *or*
2. In combination with cyclophosphamide and dexamethasone; *or*
3. In combination with lenalidomide and dexamethasone; *or*
4. In combination with daratumumab and dexamethasone for relapsed or progressive disease; *or*
5. In combination with panobinostat for members who have received at least two prior therapies, including bortezomib and an immunomodulatory agent; *or*
6. In combination with pomalidomide and dexamethasone for members who have received at least two prior therapies, including an immunomodulatory agent and a proteasome inhibitor; *or*
7. In combination with cyclophosphamide, thalidomide, and dexamethasone for relapsed or progressive disease; *or*
8. In combination with isatuximab-irfc and dexamethasone when the member has received at least one prior therapy; *or*
9. As a single agent when the member has received one or more lines of therapy;

B. *Waldenstrom's macroglobulinemia /lymphoplasmacytic lymphoma*

For treatment of Waldenstrom macroglobulinemia / lymphoplasmacytic lymphoma when the requested medication will be used as a component of CaRD (carfilzomib, rituximab, and dexamethasone) regimen.

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational and Background sections).

II. **Continuation of Therapy**

Aetna considers continued carfilzomib therapy medically necessary for members with an indication listed in Section I when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

See also CPB 0675 - Bortezomib (Velcade) (../600_699/0675.html).

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

For all indications, dosing does not exceed the following:

1. If using twice weekly: 56 mg/m^2 (not to exceed 124 mg) per dose, not to exceed 6 doses per 28 days
2. If using once weekly: 70 mg/m^2 (not to exceed 154 mg) per dose, not to exceed 3 doses per 28 days.

Below includes dosing recommendations as per the FDA-approved prescribing information.

Carfilzomib is available as Kyprolis in 60 mg sterile lyophilized powder vials.

There are varying dose recommendations for Kyprolis for multiple myeloma, depending on line of therapy and combination with other agents. Please consult specific reference for more complete dosing information. Here is an overview from the Prescribing Information:

Hydrate prior to and following Kyprolis administration as needed. Premedicate Kyprolis infusions with dexamethasone prior to all Cycle 1 doses and if infusion reaction symptoms develop or reappear.

Kyprolis plus Dexamethasone: 20/70 mg/m^2 once weekly. 30 minute infusion time.

Kyprolis plus Dexamethasone, or Monotherapy: 20/56 mg/m^2 twice weekly. 30 minute infusion time.

Kyprolis, Lenalidomide, and Dexamethasone, or Monotherapy: 20/27 mg/m^2 twice weekly. 30 minute infusion time.

There are varying dose recommendations for Kyprolis for Waldenstrom's macroglobulinemia, depending on line of therapy and combination with other agents. Please consult specific reference for more complete dosing information.

Source: Onyx, 2020.

Experimental and Investigational

Aetna considers Kyprolis (carfilzomib) therapy experimental and investigational for members receiving concomitant therapy with a proteasome inhibitor because the safety and effectiveness of this combination has not been established.

Aetna considers carfilzomib injection experimental and investigational for the treatment of the following conditions (not an all-inclusive list) because its effectiveness for these indications has not been established:

- Antibody-mediated rejection of the pulmonary allograft
- Breast cancer
- Childhood acute leukemia (e.g., acute lymphoblastic leukemia and acute myeloid leukemia)
- Chronic lymphocytic leukemia
- Diffuse large B-cell lymphoma

- Familial dysautonomia
- Glioblastoma
- Head and neck cancer
- Ischemic brain injury
- Lung cancer (e.g., non-small cell lung cancer and small cell lung cancer)
- Mantle cell lymphoma
- Neuroblastoma
- Non-Hodgkin's lymphoma
- Osteoporosis
- Osteosarcoma
- Ovarian cancer
- Pancreatic cancer
- Soft tissue sarcoma (e.g., liposarcoma)
- Small lymphocytic lymphoma
- Solitary plasmacytomas
- Smoldering myeloma (asymptomatic)
- Systemic lupus erythematosus.

Background

U.S. Food and Drug Administration (FDA)-Approved Indications

- Kyprolis is indicated in combination with dexamethasone, with lenalidomide plus dexamethasone, or with daratumumab and dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.
- Kyprolis is indicated as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

Compendial Uses

- Waldenström macroglobulinemia/lymphoplasmacytic lymphoma

Kyprolis (carfilzomib) is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. The proteasome, a multi-catalytic protease present in all eukaryotic cells, plays an important role in the regulation of cell cycle, neoplastic growth, and metastasis. Proteasome inhibitors (PIs) specifically induce apoptosis in cancer cells. Bortezomib as first-in-class PI has proven to be highly effective in some hematological malignancies, overcomes conventional chemoresistance, directly induces cell cycle arrest and apoptosis, and also targets the tumor microenvironment.

Kyprolis (carfilzomib) is a proteasome inhibitor indicated for in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy. Carfilzomib is indicated as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

It has been approved by the Food and Drug administration (FDA) for relapsed multiple myeloma (MM). Combination chemotherapy regimens have been developed providing high remission rates and remission quality in frontline treatment or in the relapsed setting in MM. The combination of proteasome inhibition with novel targeted therapies is an emerging field in oncology. Moreover, novel PIs such as carfilzomib (a selective PI that binds irreversibly to its target) have been developed (Sterz et al, 2008).

Warnings and Precautions

- *Cardiac Arrest, Congestive Heart Failure, Myocardial Ischemia*

  Death due to cardiac arrest has occurred within a day of Kyprolis (carfilzomib) administration. New onset or worsening of pre-existing congestive heart failure with decreased left ventricular function or myocardial ischemia have occurred following administration of Kyprolis (carfilzomib). Monitor for cardiac complications and manage promptly. Withhold Kyprolis

(carfilzomib) for Grade 3 or 4 cardiac events until recovery and consider whether to restart Kyprolis (carfilzomib) based on a benefit/risk assessment. Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications.

- *Pulmonary Hypertension*

  Pulmonary arterial hypertension (PAH) was reported in 2% of patients treated with Kyprolis (carfilzomib) and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Withhold Kyprolis (carfilzomib) for pulmonary hypertension until resolved or returned to baseline and consider whether to restart Kyprolis (carfilzomib) based on a benefit/risk assessment.

- *Pulmonary Complications*

  Dyspnea was reported in 35% of patients enrolled in clinical trials. Grade 3 dyspnea occurred in 5%; no Grade 4 events, and 1 death (Grade 5) was reported. Monitor and manage dyspnea immediately; interrupt Kyprolis (carfilzomib) until symptoms have resolved or returned to baseline.

- *Infusion Reactions*

  Infusion reactions were characterized by a spectrum of systemic symptoms including fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of Kyprolis (carfilzomib). Administer dexamethasone prior to Kyprolis (carfilzomib) to reduce the incidence and severity of reactions. Inform patients of the risk and symptoms and to contact physician if symptoms of an infusion reaction occur.

- *Tumor Lysis Syndrome*

  Tumor lysis syndrome (TLS) occurred following Kyprolis (carfilzomib) administration in <1% of patients. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS. Prior to receiving Kyprolis (carfilzomib), ensure that patients are well hydrated. Monitor for evidence of TLS during treatment, and manage promptly. Interrupt Kyprolis (carfilzomib) until TLS is resolved.

- *Thrombocytopenia*

  Kyprolis (carfilzomib) causes thrombocytopenia with platelet nadirs occurring around Day 8 of each 28-day cycle and recovery to baseline by the start of the next 28-day cycle. In patients with multiple myeloma, 36% of patients experienced thrombocytopenia, including Grade 4 in 10%. Thrombocytopenia following Kyprolis (carfilzomib) administration resulted in a dose reduction in 1% of patients and discontinuation of treatment with KYPROLIS in < 1% of patients. Monitor platelet counts frequently during treatment with Kyprolis (carfilzomib). Reduce or interrupt dose as clinically indicated.

- *Hepatic Toxicity and Hepatic Failure*

  Cases of hepatic failure, including fatal cases, have been reported (< 1%). Kyprolis (carfilzomib) can cause elevations of serum transaminases and bilirubin. Withhold Kyprolis (carfilzomib) in patients experiencing Grade 3 or greater elevations of transaminases, bilirubin, or other liver abnormalities until resolved or returned to baseline. After resolution, consider if restarting Kyprolis (carfilzomib) is appropriate. Monitor liver enzymes frequently.

- *Posterior Reversible Encephalopathy Syndrome (PRES)*

  PRES, formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS), is a neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered

consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging (MRI). Cases of PRES have been reported in patients receiving KYPROLIS. Discontinue KYPROLIS if PRES is suspected and evaluate. The safety of reinitiating KYPROLIS therapy in patients previously experiencing PRES is not known.

- *Embryo-fetal Toxicity*

  Kyprolis (carfilzomib) can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using Kyprolis (carfilzomib). Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis (carfilzomib). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Vij et al (2012) stated that in phase 1 studies, carfilzomib elicited promising responses and an acceptable toxicity profile in patients with relapsed and/or refractory MM (R/R MM). In the present phase 2, multi-center, open-label study, 129 bortezomib-naive patients with R/R MM (median of 2 prior therapies) were separated into cohort 1, scheduled to receive intravenous carfilzomib 20 mg/m(2) for all treatment cycles, and cohort 2, scheduled to receive 20 mg/m(2) for cycle 1 and then 27 mg/m(2) for all subsequent cycles. The primary end point was an overall response rate [ORR] (greater than or equal to partial response) of 42.4 % in cohort 1 and 52.2 % in cohort 2. The clinical benefit response (ORR + minimal response) was 59.3 % and 64.2 % in cohorts 1 and 2, respectively. Median duration of response was 13.1 months and not reached, and median time to progression was 8.3 months and not reached, respectively. The most common treatment-emergent adverse events (AEs) were fatigue (62.0 %) and nausea (48.8 %). Single-agent carfilzomib elicited a low incidence of peripheral neuropathy (PN) – 17.1

% overall (1 grade 3; no grade 4) – in these pretreated bortezomib-naive patients. The authors concluded that the findings of the present study support the use of carfilzomib in R/R MM patients.

In an open-label, single-arm phase 2 study, Siegel et al (2012) examined the effects of carfilzomib in patients with relapsed and refractory MM. Participants received carfilzomib 20 mg/m(2) intravenously twice-weekly for 3 of 4 weeks in cycle 1, then 27 mg/m(2) for less than or equal to 12 cycles. The primary endpoint was ORR (greater than or equal to partial response). Secondary endpoints included clinical benefit response rate (greater than or equal to minimal response), duration of response, progression-free survival, overall survival, and safety. A total of 266 patients were evaluable for safety, 257 for efficacy; 95 % were refractory to their last therapy; 80 % were refractory or intolerant to both bortezomib and lenalidomide. Patients had median of 5 prior lines of therapy, including bortezomib, lenalidomide, and thalidomide. Overall response rate was 23.7 % with median duration of response of 7.8 months. Median overall survival was 15.6 months. Adverse events were manageable without cumulative toxicities. Common AEs were fatigue (49 %), anemia (46 %), nausea (45 %), and thrombocytopenia (39 %); 33 patients (12.4 %) experienced PN, primarily grades 1 or 2; and 33 patients (12.4 %) withdrew because of an AE. Durable responses and an acceptable tolerability profile in this heavily pretreated population demonstrated the potential of carfilzomib to offer meaningful clinical benefit.

Buac et al (2013) noted that bortezomib is the first FDA-approved PI used as a frontline treatment for newly diagnosed MM, relapsed/refractory MM and mantle cell lymphoma. Though successful in improving clinical outcomes for patients with hematological malignancies, relapse often occurs in those who initially responded to bortezomib. Thus, the acquisition of bortezomib resistance is a major issue with its therapy. Furthermore, some neuro-toxicities have been associated with bortezomib treatment and its efficacy in solid tumors is lacking. These observations have encouraged researchers to pursue the next generation of PIs, which would ideally overcome bortezomib resistance, have reduced toxicities and a broader range of anti-cancer activity. The authors described recent advances in the field, including, and most notably, the most recent FDA approval of carfilzomib a second generation PI.

Thompson (2013) reviewed and summarized data on carfilzomib, which was approved by the FDA in July 2012 for the treatment of patients with relapsed and refractory MM who received prior bortezomib and thalidomide or lenalidomide. A literature search through PubMed was conducted through October 2012 using the terms carfilzomib, PR-171, proteasome inhibitor (PI), and MM. Data were also obtained through the American Society of Clinical Oncology and American Society of Hematology abstracts and FDA briefing documents. The literature search was limited to human studies published in English. Priority was placed on trials of carfilzomib in relapsed and refractory MM. Carfilzomib is a new PI that differs in pharmacology and pharmacokinetics from bortezomib, the first-in-class PI. The FDA approval was based on efficacy data from a phase 2 study of carfilzomib in patients with relapsed and refractory MM (n = 266). All patients had received prior bortezomib and 80 % were refractory or intolerant to both bortezomib and lenalidomide.

On July 20, 2012, the Food and Drug Administration approved carfilzomib injection (Kyprolis, Onyx Pharmaceuticals), for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent (e.g., thalidomide or lenalidomide), and have demonstrated disease progression on or within 60 days of the completion of the last therapy. The approval was based on the results of a single-arm, multi-center clinical trial enrolling 266 patients with relapsed MM who had received at least 2 prior therapies, including bortezomib and an immunomodulatory agent (thalidomide or lenalidomide). To reduce the incidence and severity of infusion reactions associated with carfilzomib administration, dexamethasone (4 mg orally or intravenously) was administered prior to all carfilzomib doses during the first cycle and prior to all carfilzomib doses during the first dose-escalation (27 mg/m2) cycle. Dexamethasone pre-medication was re-instated if these symptoms re-appeared during subsequent cycles. The primary efficacy endpoint was ORR, determined by Independent Review Committee assessment using International Myeloma Working Group criteria. The ORR was 22.9 % (95 % confidence interval [CI]: 18.0 to 28.5), consisting of 1 complete response, 13 very good partial responses and 47 partial responses. The median response duration was 7.8 months (95 % CI: 5.6 to 9.2). Safety data was evaluated in 526 patients with relapsed MM who received carfilzomib as monotherapy. Patients received a median of 4 treatment cycles with a

median cumulative carfilzomib dose of 993.4 mg. The most common AEs (incidence of 30 % or greater) observed in clinical trials of patients with MM were fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia. Serious adverse reactions were reported in 45 % of patients. The most common serious AEs were pneumonia, acute renal failure, pyrexia, and congestive heart failure. There were 37/526 (7 %) deaths on study. The most common causes of death, other than underlying disease, were cardiac (5 patients), end-organ failure (4 patients), and infection (4 patients). As a condition of accelerated approval, Onyx will submit the complete analysis of an ongoing randomized phase 3 trial comparing lenalidomide plus low-dose dexamethasone to lenalidomide plus low-dose dexamethasone plus carfilzomib. The primary endpoint of this trial is progression-free survival, with enrollment of patients with relapsed or refractory MM after 1 to 3 prior therapies.

Carfilzomib should be administered intravenously over 2 to 10 mins, on 2 consecutive days weekly (for 3 weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12 day rest period (days 17 to 28). Recommended cycle one dose is 20 mg/m2/day, and, if tolerated, the recommended dose for the second and succeeding cycles is 27 mg/ m2/day.

Multiple Myeloma

Wang et al (2013) previously reported a phase Ib dose-escalation study of carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in relapsed or progressive MM where the maximum planned dose (MPD) was carfilzomib 20 mg/m2 days 1 and 2 of cycle 1 and 27 mg/m2 days 8, 9, 15, 16, and thereafter; lenalidomide 25 mg days 1 to 21; and dexamethasone 40 mg once-weekly on 28-day cycles. Wang et al (2013) presented the results from the phase II dose expansion at the MPD, focusing on the 52 patients enrolled in the MPD cohort. Median follow-up was 24.4 months. In the MPD cohort, overall response rate (ORR) was 76.9 % with median time to response of 0.95 month (range of 0.5 to 4.6) and duration of response (DOR) of 22.1 months. Median progression-free survival (PFS) was 15.4 months; ORR was 69.2 % in bortezomib-refractory patients and 69.6 % in lenalidomide-refractory patients with median DOR of 22.1 and 10.8 months, respectively. A median of 9.5 (range of 1 to 45) carfilzomib cycles were started with 7.7 % of patients

requiring carfilzomib dose reductions and 19.2 % discontinuing CRd due to adverse events (AEs). Grade 3/4 AEs included lymphopenia (48.1 %), neutropenia (32.7 %), thrombocytopenia (19.2 %), and anemia (19.2 %). The investigators reported that CRd at the MPD was well-tolerated with robust, rapid, and durable responses.

Waldenstrom Macroglobulinemia

Issa et al (2011) stated that based on the understanding of the complex interaction between Waldenstrom macroglobulinemia (WM) tumor cells and the bone marrow microenvironment, and the signaling pathways that are deregulated in WM pathogenesis, a number of novel therapeutic agents are now available and have demonstrated significant efficacy in WM. The range of the ORR for these novel agents is between 25 and 96 %. Ongoing and planned future clinical trials include those using protein kinase C inhibitors such as enzastaurin, new PIs such as carfilzomib, histone deacetylase inhibitors such as LBH589, humanized CD20 antibodies such as ofatumumab and additional alkylating agents such as bendamustine. These agents, when compared with traditional chemotherapeutic agents, may lead in the future to higher responses, longer remissions and better quality of life for patients with WM.

Treon et al (2014) found that carfilzomib, rituximab and dexamethasone (CaRD) offers a neuropathy sparing approach for proteasome inhibitor based therapy for Waldenstrom’s macroglobulinemia. Bortezomib frequently produces severe treatment-related peripheral neuropathy (PN) in Waldenström's macroglobulinemia (WM). Carfilzomib is a neuropathy-sparing proteasome inhibitor. Treon et al (2014) examined carfilzomib, rituximab, and dexamethasone (CaRD) in symptomatic WM patients naïve to bortezomib and rituximab. Protocol therapy consisted of intravenous carfilzomib, 20 mg/m2 (cycle 1) and 36 mg/m(2) (cycles 2 to 6), with intravenous dexamethasone, 20 mg, on days 1, 2, 8, and 9, and rituximab, 375 mg/m(2), on days 2 and 9 every 21 days. Maintenance therapy followed 8 weeks later with intravenous carfilzomib, 36 mg/m(2), and intravenous dexamethasone, 20 mg, on days 1 and 2, and rituximab, 375 mg/m(2), on day 2 every 8 weeks for 8 cycles. Overall response rate was 87.1 % (1 complete response, 10 very good partial responses [PR], 10 PR, and 6 minimal responses) and was not impacted by MYD88(L265P) or CXCR4(WHIM) mutation status. With a median follow-

up of 15.4 months, 20 patients remained progression free. Grade greater than or equal to 2 toxicities included asymptomatic hyperlipasemia (41.9 %), reversible neutropenia (12.9 %), and cardiomyopathy in 1 patient (3.2 %) with multiple risk factors, and PN in 1 patient (3.2 %) which was grade 2. The investigators noted that declines in serum IgA and IgG were common.

Antibody-Mediated Rejection of the Pulmonary Allograft

Ensor and colleagues (2017) presented the findings of an observational study of lung transplant recipients (LTR) treated with carfilzomib (CFZ)-based therapy for antibody-mediated rejection (AMR) of the lung. Patients were considered responders to CFZ if complement-1q (C1q)-fixing ability of their immuno-dominant (ID) donor-specific anti-human leukocyte antibody (DSA) was suppressed after treatment. Treatment consisted of CFZ plus plasma exchange and immunoglobulins. A total of 14 LTRs underwent CFZ for 20 ID DSA AMR; 10 (71.4 %) of LTRs responded to CFZ. DSA IgG mean fluorescence intensity (MFI) fell from 7,664 (inter-quartile range [IQR] 3,230 to 11,874) to 1,878 (653 to 7,791) after therapy (p = 0.001) and to 1,400 (850 to 8,287) 2 weeks later (p = 0.001). DSA C1q MFI fell from 3,596 (IQR 714 to 14,405) to less than 30 after therapy (p = 0.01) and less than 30 2 weeks later (p = 0.02). Forced expiratory volume in 1 second (FEV1) fell from mean 2.11 liters (L) pre-AMR to 1.92 L at AMR (p = 0.04). FEV1 was unchanged after CFZ (1.91 L) and subsequently rose to a maximum of 2.13 L (p = 0.01). Mean forced expiratory flow during mid forced vital capacity (25-75) (FEF25-75) fell from mean 2.5 L pre-AMR to 1.95 L at AMR (p = 0.01). FEF25-75 rose after CFZ to 2.54 L and reached a maximum of 2.91 L (p = 0.01). Responders had less chronic lung allograft dysfunction or progression versus non-responders (25 % versus 83 %, p = 0.04). No deaths occurred within 120 days and 7 patients died post CFZ therapy of allograft failure. The authors concluded that larger prospective interventional studies are needed to further describe the benefit of CFZ-based therapy for pulmonary AMR.

B-Cell Lymphomas, Including Mantle Cell Lymphoma

Dasmahapatra et al (2012) reported that in-vivo administration of carfilzomib and obatoclax to mice inoculated with SUDHL4 cells substantially suppressed tumor growth, activated JNK, inactivated AKT, and increased survival compared with the effects of single-agent treatment. Together, these findings argued that a strategy combining carfilzomib and obatoclax warrants attention in diffuse large B-cell lymphoma.

Mato et al (2012) stated that bortezomib is approved for the treatment of relapsed or refractory mantle cell lymphoma. The mechanisms of proteasome inhibition are very complex by nature and not fully understood. However, mechanisms of action shared by bortezomib and PIs such as carfilzomib are distinct from those of other non-Hodgkin's lymphoma (NHL) treatments, making them attractive options for combination therapy. Pre-clinical evidence suggested that the PIs have additive and/or synergistic activity with a large number of agents both in-vitro and in-vivo, from cytotoxics to new biologicals, supporting a growing number of combination studies currently underway in NHL patients. The authors concluded that the results of these studies will help the understanding about how to best integrate proteasome inhibition in the management of NHL and continue to improve patient outcomes.

Holkova et al (2016) performed a phase I clinical trial with carfilzomib and vorinostat in 20 B-cell lymphoma patients. Vorinostat was given orally twice-daily on days 1, 2, 3, 8, 9, 10, 15, 16, and 17 followed by carfilzomib (given as a 30-min infusion) on days 1, 2, 8, 9, 15, and 16. A treatment cycle was 28 days. Dose escalation initially followed a standard 3+3 design, but adapted a more conservative accrual rule following dose de-escalation. The maximum tolerated dose (MTD) was 20 mg/m2 carfilzomib and 100 mg vorinostat (twice-daily). The dose-limiting toxicities (DLTs) were grade 3 pneumonitis, hyponatremia, and febrile neutropenia. One patient had a PR and 2 patients had stable disease (SD). Correlative studies showed a decrease in NF-κB activation and an increase in Bim levels in some patients, but these changes did not correlate with clinical response.

Dasmahapatra et al (2011) noted that carfilzomib/vorinostat co-administration resulted in a pronounced reduction in tumor growth compared with single agent treatment in a mantle cell lymphoma

xenograft model associated with enhanced apoptosis, λH2A.X formation, and JNK activation. The authors concluded that these findings suggested that regimens of carfilzomib/histone deacetylase inhibitors warrant attention in mantle cell lymphoma.

Lee and colleagues (2019) noted that between September 2014 and August 2016, 6 patients were enrolled in an Institutional Review Board-approved single institutional prospective phase-II clinical trial of carfilzomib in patients with relapsed/refractory mantle cell lymphoma (MCL). Inclusion criteria were a diagnosis of MCL based on histopathological features and positive staining for CD20 and CCND1. Patients were required to be greater than or equal to 18 years of age with measurable disease as per the International Harmonization Project on Lymphoma 2007 criteria, have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, and show adequate bone marrow, live, and renal functions. Carfilzomib was given at a dose of 20*/56 mg/m2 (*carfilzomib 20 mg/m2 IV on days 1 and 2 in cycle 1 followed by 56 mg/m2 for each subsequent dose thereafter) on days 1 and 2, 8 and 9, 15 and 16 of a 28-day cycle. Following cycle 12, carfilzomib was given on days 1 and 2 and 15 and 16 only. Of 6 patients who signed consent for enrolment, only 4 were actually dosed, as 2 patients withdrew consent prior to initiation of therapy. Of 4 patients who started therapy, 2 progressed prior to the start of cycle 2 and 2 patients progressed prior to cycle. Only 4 patients received the drug before the study was closed due to a slow rate of accrual. Thus, the authors acknowledged the limitation of comparison between different diseases. The authors concluded that carfilzomib appeared to be safe; however, more patients are needed to make a more definitive conclusion about its activity in MCL.

Breast Cancer

Busonero and colleagues (2018) stated that most cases of breast cancer (BC) are estrogen receptor α-positive (ERα+) at diagnosis. The presence of ERα drives the therapeutic approach for this disease, which often consists of endocrine therapy (ET). 4OH-Tamoxifen and faslodex (i.e., fulvestrant - ICI182,780) are 2 ETs that render tumor cells insensitive to 17β-estradiol (E2)-dependent proliferative stimuli and prevent BC progression. However, ET has limitations and serious failures in different

tissues and organs. Thus, there is an urgent need to identify novel drugs to fight BC. Re-positioning of old drugs for new clinical purposes is an attractive alternative for drug discovery. For this analysis, these researchers focused on the modulation of intracellular ERα levels in BC cells as target for the screening of about 900 FDA-approved compounds that would hinder E2:ERα signaling and inhibit BC cell proliferation. They found that carfilzomib induces ERα degradation and prevents E2 signaling and cell proliferation in 2 ERα+ BC cell lines. Remarkably, the analysis of carfilzomib effects on a cell model system with an acquired resistance to 4OH-tamoxifen revealed that this drug has an anti-proliferative effect superior to faslodex in BC cells. The authors concluded that these findings identified carfilzomib as a drug preventing E2:ERα signaling and cell proliferation in BC cells and suggested its possible re-position for the treatment of ERα+ BC as well as for those diseases that have acquired resistance to 4OH-tamoxifen.

Park and colleagues (2019) noted that CFZ is the second-in-class proteasome inhibitor with much improved efficacy and safety profiles over bortezomib in MM patients. In expanding the utility of CFZ to solid cancer therapy, the poor aqueous solubility and in-vivo instability of CFZ are considered major drawbacks. These investigators examined if a nano-crystal (NC) formulation can address these issues and enhance anti-cancer efficacy of CFZ against breast cancer. The surface of NC was coated with albumin in order to enhance the formulation stability and drug delivery to tumors via interactions with albumin-binding proteins located in and near cancer cells. The novel albumin-coated NC formulation of CFZ (CFZ-alb NC) displayed improved metabolic stability and enhanced cellular interactions, uptake and cytotoxic effects in breast cancer cells in-vitro. Consistently, CFZ-alb NC showed greater anti-cancer efficacy in a murine 4T1 orthotopic breast cancer model than the currently used cyclodextrin-based formulation. The authors concluded that these findings demonstrated the potential of CFZ-alb NC as a viable formulation for breast cancer therapy.

Childhood Acute Leukemia

Annesley and Brown (2015) stated that acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) make up approximately 1/3 of all pediatric cancer diagnoses. Despite remarkable improvement in the

treatment outcomes of these diseases over the past several decades, the prognosis for certain high-risk groups of leukemia and for relapsed disease remains poor. However, recent insights into different types of "driver" lesions of leukemogenesis, such as the aberrant activation of signaling pathways and various epigenetic modifications, have led to the discovery of novel agents that specifically target the mechanism of transformation. In parallel, emerging approaches in cancer immunotherapy have led to newer therapies that can exploit and harness cytotoxic immunity directed against malignant cells. These researchers reviewed the rationale and implementation of recent and specifically targeted therapies in acute pediatric leukemia. Topics covered include the inhibition of critical cell signaling pathways [BCR-ABL, FMS-like tyrosine kinase 3 (FLT3), mammalian target of rapamycin (mTOR), and Janus-associated kinase (JAK)], proteasome inhibition (e.g., carfilzomib), inhibition of epigenetic regulators of gene expression [DNA methyltransferase (DNMT) inhibitors, histone deacetylase (HDAC) inhibitors, and disruptor of telomeric signaling-1 (DOT1L) inhibitors], monoclonal antibodies and immuno-conjugated toxins, bispecific T-cell engaging (BiTE) antibodies, and chimeric antigen receptor-modified (CAR) T cells.

Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)

Awnan and colleagues (2015) noted that the proteasome complex degrades proteins involved in a variety of cellular processes and is a powerful therapeutic target in several malignancies. Carfilzomib (CFZ) is a potent proteasome inhibitor which induces rapid chronic lymphocytic leukemia (CLL) cell apoptosis in-vitro. These researchers conducted a phase I dose-escalation clinical trial to determine the safety and tolerability of CFZ in relapsed/refractory CLL or small lymphocytic lymphoma (SLL). A total of 19 patients were treated with CFZ initially at 20 mg/m2; then escalated in 4 cohorts (27, 36, 45 and 56 mg/m2) on days 1, 2, 8, 9, 15 and 16 of 28-day cycles. Therapy was generally well-tolerated, and no DLTs were observed. The most common hematologic toxicities were thrombocytopenia and neutropenia. All patients evaluable for response had SD, including patients with del17p13 and fludarabine-resistant disease. The authors concluded that the findings of this trial

showed acceptable tolerability and limited preliminary efficacy of CFZ in CLL and SLL. These preliminary findings need to be validated in well-designed studies.

Familial Dysautonomia

Herve and Ibrahim (2017) stated that familial dysautonomia (FD) is a rare neurodegenerative disorder caused by a mutation of the IKBKAP gene, which induces low expression levels of the Elongator subunit IKAP/hELP1 protein. A rational strategy for FD treatment could be to identify drugs increasing IKAP/hELP1 expression levels by blocking protein degradation pathways such as the 26S proteasome. Proteasome inhibitors are promising molecules emerging in cancer treatment and could thus constitute an enticing pharmaceutical strategy for FD treatment. Therefore, these researchers tested 3 proteasome inhibitors on FD human olfactory ecto-mesenchymal stem cells (hOE-MSCs): 2 approved by the FDA and European Medicines Agency (EMA), bortezomib and carfilzomib, as well as epoxomicin. Although all 3 inhibitors demonstrated activity in correcting IKBKAP mRNA aberrant splicing, carfilzomib was superior in enhancing IKAP/hELP1 quantity. Moreover, these researchers observed a synergistic effect of suboptimal doses of carfilzomib on kinetin in improving IKBKAP isoforms ratio and IKAP/hELP1 expression levels allowing to counterbalance carfilzomib toxicity. Finally, these investigators identified several dysregulated miRNAs after carfilzomib treatment that target proteasome-associated mRNAs and determined that IKAP/hELP1 deficiency in FD pathology is correlated to an over-activity of the 26S proteasome. The authors concluded that these findings reinforce the rationale for using chemical compounds inhibiting the 26S proteasome as an innovative option for the treatment of FD and a promising therapeutic pathway for many other neurodegenerative diseases. These preliminary findings need to be validated by well-designed clinical studies.

Glioblastoma

Zhang and colleagues (2018) noted that the robust proliferation of tumors relies on a rich neovasculature for nutrient supplies. Thus, a basic strategy of tumor targeting therapy should include not only killing regular cancer cells but also blocking tumor neovasculature. D-peptide DA7R,

which was previously reported to specifically bind vascular endothelial growth factor receptor 2 (VEGFR2) and neuropilin-1 (NRP-1), could achieve the goal of multi-target recognition. Accordingly, the main purposes of this work were to establish a carfilzomib-loaded lipid nanodisk modified with multi-functional peptide DA7R (DA7R-ND/CFZ) and to evaluate its anti-glioblastoma efficacy in-vitro and in-vivo. It was testified that the DA7R peptide-conjugated lipid nanodisk could be specifically taken up by U87MG cells and HUVECs. Furthermore, DA7R-ND demonstrated a more enhanced penetration than that of the non-modified formulation on the tumor spheroid model in-vitro and more tumor region accumulation in-vivo on the subcutaneous and intracranial tumor-bearing nude mice model. DA7R-ND was shown to co-localize with tumor neovasculature in-vivo. When loaded with proteasome inhibitor carfilzomib, the DA7R-decorated nanodisk could remarkably suppress tumor proliferation, extend survival time of nude mice bearing an intracranial tumor, and inhibit neovasculature formation with an efficacy higher than that of the non-modified nanodisk in-vitro and in-vivo. The authors concluded that the present study verified that the heptapeptide DA7R-conjugated nanodisk is a promising nano-carrier for glioblastoma targeting therapy.

Graft-Versus-Host Disease

Shimoni and colleagues (2020) noted that acute graft-versus-host disease (aGVHD) is the major treatment-related complication following stem-cell transplantation (SCT) from unrelated donors. The proteasome-inhibitor bortezomib was added to GVHD prevention regimens with initial promise. However, 2 randomized studies failed to show efficacy. These researchers examined the addition of carfilzomib (20 mg/m2, intravenously on days +1 and +2) to cyclosporine/methotrexate backbone in 26 patients after SCT from unrelated donors. They compared outcomes to historical group of 100 patients given cyclosporine/methotrexate alone. Median follow-up was 34 months. There was no difference between the groups in engraftment or toxicities. The cumulative incidence of aGVHD grade II to IV, 6 months post-transplant was 11 % (95 % CI: 4 to 32) and 39 % (95 % CI: 30 to 50), respectively (p = 0.01). The cumulative incidence of chronic GVHD (cGVHD), 2 years post-transplant, was 49 % (95 % CI: 32 to 75) and 41 % (95 % CI: 33 to 52), respectively (p = 0.98); 3-year non-relapse

mortality (NRM) was 11 % (95 % CI: 4 to 33) and 18 % (95 % CI: 12 to 27, p = 0.45) while 3-year relapse rates were 8 % (95 % CI: 2 to 29) and 26 % (95 % CI: 18 to 36), respectively (p = 0.06); 3-year survival was 81 % (95 % CI: 66 to 96) and 56 % (95 % CI: 46 to 66), respectively (p = 0.05). The authors concluded that carfilzomib with cyclosporine/methotrexate was safe, may reduce aGVHD, and possibly improve survival after unrelated donor SCT. Moreover, these researchers stated that these initial findings merit further study in larger comparative studies.

Ischemic Brain Injury

Wu and colleagues (2020) stated that mitophagy, the elimination of damaged mitochondria through autophagy, promotes neuronal survival in cerebral ischemia. Previous studies found deficient mitophagy in ischemic neurons, but the mechanisms are still largely unknown. These researchers determined that BNIP3L/NIX, a mitophagy receptor, was degraded by proteasomes, which led to mitophagy deficiency in both ischemic neurons and brains. BNIP3L exists as a monomer and homodimer in mammalian cells, but the effects of homodimer and monomer on mitophagy are unclear. Site-specific mutations in the trans-membrane domain of BNIP3L (S195A and G203A) only formed the BNIP3L monomer and failed to induce mitophagy. Moreover, over-expression of wild-type BNIP3L, in contrast to the monomeric BNIP3L, rescued the mitophagy deficiency and protected against cerebral ischemic injury. The macro-autophagy/autophagy inhibitor 3-MA and the proteasome inhibitor MG132 were used in cerebral ischemic brains to identify how BNIP3L was reduced. These investigators found that MG132 blocked the loss of BNIP3L and subsequently promoted mitophagy in ischemic brains. Furthermore, the dimeric form of BNIP3L was more prone to be degraded than its monomeric form. Carfilzomib reversed the BNIP3L degradation and restored mitophagy in ischemic brains. This treatment protected against either acute or chronic ischemic brain injury. Remarkably, these effects of carfilzomib were abolished in bnip3l -/- mice. The authors concluded that the findings of this study linked BNIP3L degradation by proteasomes with mitophagy deficiency in cerebral ischemia. They proposed carfilzomib as a novel therapy to rescue ischemic brain injury by preventing BNIP3L degradation.

Lung Cancer

Baker et al (2014) stated that CFZ has been FDA-approved for the treatment of relapsed and refractory MM. Phase 1B studies of CFZ reported signals of clinical activity in solid tumors, including small cell lung cancer (SCLC). These researchers investigated the activity of CFZ in lung cancer models. A diverse panel of human lung cancer cell lines and a SHP77 SCLC xenograft model were used to investigate the anti-tumor activity of CFZ. Carfilzomib treatment inhibited both the constitutive proteasome and the immune-proteasome in lung cancer cell lines; CFZ had marked anti-proliferative activity in A549, H1993, H520, H460, and H1299 non-small cell lung cancer (NSCLC) cell lines, with half maximal inhibitory concentration (IC50) values after 96 hour exposure from less than 1.0 nM to 36 nM. Carfilzomib had more variable effects in the SHP77 and DMS114 SCLC cell lines, with IC50 values at 96 hours from less than 1 nM to 203 nM. Western blot analysis of CFZ-treated H1993 and SHP77 cells showed cleavage of poly ADP ribose polymerase (PARP) and caspase-3, indicative of apoptosis, and induction of microtubule-associated protein-1 light chain-3B (LC3B), indicative of autophagy. In SHP77 flank xenograft tumors, CFZ monotherapy inhibited tumor growth and prolonged survival, while no additive or synergistic anti-tumor efficacy was observed for CFZ + cisplatin (CDDP). The authors concluded that CFZ demonstrated anti-proliferative activity in lung cancer cell lines in-vitro and resulted in a significant survival advantage in mice with SHP77 SCLC xenografts, supporting further pre-clinical and clinical investigations of CFZ in NSCLC and SCLC.

In a phase I clinical trial (Arnold et al, 2017) carfilzomib was combined with irinotecan to provide a synergistic approach in relapsed, irinotecan-sensitive cancers including lung cancer. Patients with relapsed irinotecan-sensitive cancers received carfilzomib (day 1, 2, 8, 9, 15, and 16) at 3 dose levels (20/27 mg/m2, 20/36 mg/m2, and 20/45 mg/m2/day) in combination with irinotecan (days 1, 8 and 15) at 125 mg/m2/day. Key eligibility criteria included measurable disease, a Zubrod PS of 0 or 1, and acceptable organ function. Patients with stable asymptomatic brain metastases were eligible. Dose escalation utilized a standard 3 + 3 design. A total of 16 patients were enrolled to 3 dose levels, with 4 patients replaced; 3 patients experienced DLT and the MTD was exceeded in Cohort 3. The RP2 dose was carfilzomib 20/36 mg/m2

(given on days 1, 2, 8, 9, 15, and 16) and irinotecan 125 mg/m2 (days 1, 8 and 15). Common grade (Gr) 3 and 4 toxicities included fatigue (19 %), thrombocytopenia (19 %), and diarrhea (13 %). The authors concluded that irinotecan and carfilzomib were well-tolerated, with common toxicities of fatigue, thrombocytopenia and neutropenic fever. Objective clinical response was 19 % (1 confirmed PR in SCLC and 2 unconfirmed); SD was 6 % for a disease control rate (DCR) of 25 %. The authors stated that the recommended phase II dose was carfilzomib 20/36 mg/m2 and irinotecan 125 mg/m2. The phase II evaluation is ongoing in relapsed SCLC.

Neuroblastoma

Barbagallo and colleagues (2019) stated that neuroblastoma (NB) is an embryonic malignancy affecting the physiological development of adrenal medulla and paravertebral sympathetic ganglia in early infancy. Proteasome inhibitors (PIs) (i.e., carfilzomib (CFZ)) may represent a possible pharmacological treatment for solid tumors including NB. In the present study, these researchers tested the effect of a novel non-competitive inhibitor of heme oxygenase-1 (HO-1), LS1/71, as a possible adjuvant therapy for the efficacy of CFZ in neuroblastoma cells. Results showed that CFZ increased both HO-1 gene expression (about 18-fold) and HO activity (about 8-fold), following activation of the ER stress pathway. The involvement of HO-1 in CFZ-mediated cytotoxicity was further confirmed by the protective effect of pharmacological induction of HO-1, significantly attenuating cytotoxicity. In addition, HO-1 selective inhibition by a specific siRNA increased the cytotoxic effect following CFZ treatment in NB whereas SnMP, a competitive pharmacological inhibitor of HO, showed no changes in cytotoxicity. These findings suggested that treatment with CFZ produced ER stress in NB without activation of CHOP-mediated apoptosis, whereas co-treatment with CFZ and LS1/71 led to apoptosis activation and CHOP expression induction. The authors concluded that the findings of this study showed that treatment with the non-competitive inhibitor of HO-1, LS1 / 71, increased cytotoxicity mediated by CFZ, triggering apoptosis following ER stress activation. These results suggested that PIs may represent a possible pharmacological treatment for solid tumors and that HO-1 inhibition may represent a possible strategy to overcome chemo-resistance and increase the efficacy of chemotherapeutic regimens.

Oprozomib

Zang et al (2012) stated that ONX 0912 (oprozomib) is an orally bioavailable derivative of carfilzomib. The activities of carfilzomib and ONX 0912 against solid tumor malignancies are less well understood. These researchers investigated the impact and mechanisms of action of carfilzomib and ONX 0912 in pre-clinical models of head and neck squamous cell carcinoma (HNSCC). The authors concluded that carfilzomib and ONX 0912 are potently active against HNSCC cells, and the activities of these agents can be enhanced via suppression of Mcl-1 or inhibition of autophagy. They stated that oral ONX 0912 exhibits in-vivo activity against HNSCC tumors and may represent a useful therapeutic agent for this malignancy.

Osteoporosis

Yang and associates (2015) stated that parathyroid hormone (PTH) induces osteoclast formation and activity by increasing the ratio of RANKL/OPG in osteoblasts. The proteasome inhibitor CFZ has been used as an effective therapy for MM via the inhibition of pathologic bone destruction. However, the effect of combination of PTH and CFZ on osteoclastogenesis is unknown. These investigators reported that CFZ inhibits PTH-induced RANKL expression and secretion without affecting PTH inhibition of OPG expression, and it does so by blocking HDAC4 proteasomal degradation in osteoblasts. Furthermore, these investigators used different types of culture systems, including co-culture, indirect co-culture, and transactivation, to assess the effect of CFZ on PTH action to induce osteoclastogenesis. These findings demonstrated that CFZ blocks PTH-induced osteoclast formation and bone resorption by its additional effect to inhibit RANKL-mediated IκB degradation and NF-κB activation in osteoclasts. The authors concluded that this study showed for the first time that CFZ targets both osteoblasts and osteoclasts to suppress PTH-induced osteoclast differentiation and bone resorption. They stated that these findings warrant further investigation of this novel combination in animal models of osteoporosis and in patients.

Osteosarcoma

Patatsos and colleagues (2018) noted that osteosarcoma, a common malignancy in large dog breeds, typically metastasizes from long bones to lungs and is usually fatal within 1 to 2 years of diagnosis. Better therapies are needed for canine patients and their human counterparts, 1/3 of whom die within 5 years of diagnosis. These researchers compared the in-vitro sensitivity of canine osteosarcoma cells derived from 4 tumors to the currently used chemotherapy drugs doxorubicin and carboplatin, and 4 new anti-cancer drugs. Agents targeting histone deacetylases or PARP were ineffective; 2 of the 4 cell lines were somewhat sensitive to the BH3-mimetic navitoclax. The proteasome inhibitor bortezomib potently induced caspase-dependent apoptosis, at concentrations substantially lower than levels detected in the bones and lungs of treated rodents. Co-treatment with bortezomib and either doxorubicin or carboplatin was more toxic to canine osteosarcoma cells than each agent alone. Newer proteasome inhibitors carfilzomib, ixazomib, oprozomib and delanzomib manifested similar activities to bortezomib. Human osteosarcoma cells were as sensitive to bortezomib as the canine cells, but slightly less sensitive to the newer drugs. Human osteoblasts were less sensitive to proteasome inhibition than osteosarcoma cells, but physiologically relevant concentrations were toxic. Such toxicity, if replicated in-vivo, may impair bone growth and strength in adolescent human osteosarcoma patients, but may be tolerated by canine patients, which are usually diagnosed later in life. Proteasome inhibitors such as bortezomib may be useful for treating canine osteosarcoma, and ultimately may improve outcomes for human patients if their osteoblasts survive exposure in-vivo, or if osteoblast toxicity can be managed.

Ovarian Cancer

Zarei and colleagues (2019) noted that previous studies on the efficacy of platinum-based drugs and selective inhibitors of proteasome have revealed promising outcomes. These researchers examined the effects of the combination of cisplatin and CFZ on the cell death induction and drug efflux transporters expression in cisplatin-sensitive (A2780s) and cisplatin-resistant (A2780cp) ovarian cancer cells lines. MTT cytotoxic assay was conducted to determine the cytotoxicity. Drug interactions were analyzed based on Chou-Talalay's principles and real-time polymerase chain reaction)PCR) analysis was performed to determine possible alterations in mRNA levels of MRP1 and BCRP. A2780s cells

were more susceptible to both cisplatin and CFZ while analyses of drug interactions between the 2 agents showed synergistic effects in all affected fractions of drug-treated A2780s and A2780cp cells (CI < 0.9) with the combination indices being significantly lower in A2780cp cells ($p < 0.01$). These investigators also found that although mRNA levels of BCRP and MRP1 were significantly altered in both cells exposed to each drug alone, only the combination regimen was able to significantly reduce the mRNA levels of these genes in A2780cp cells ($p < 0.001$). The authors concluded that this combination might be a potential strategy for suppressing cell growth via down-regulating the drug efflux transporters expression, especially in cisplatin-resistant ovarian cancer cells.

Pancreatic Cancer

Kawaguchi and colleagues (2017) reported that a pancreatic ductal adenocarcinoma (PDAC), obtained from a patient, was grown orthotopically in the pancreatic tail of nude mice to establish a patient-derived orthotopic (PDOX) model. Seven weeks after implantation, PDOX nude mice were divided into the following groups: (i) untreated control (n = 7); (ii) gemcitabine (100 mg/kg, i.p., once-weekly for 2 weeks, n = 7); (iii) cobimetinib (5 mg/kg, p.o., 14 consecutive days, n = 7); (iv) trametinib (0.3 mg/kg, p.o., 14 consecutive days, n = 7); (v) trabectedin (0.15 mg/kg, i.v., once-weekly for 2 weeks, n = 7); (vi) temozolomide (25 mg/kg, p.o., 14 consecutive days, n = 7); (vii) carfilzomib (2 mg/kg, i.v., twice-weekly for 2 weeks, n = 7); (viii) bortezomib (1 mg/kg, i.v., twice-weekly for 2 weeks, n = 7); (ix) MK-1775 (20 mg/kg, p.o., 14 consecutive days, n = 7); (x) BEZ-235 (45 mg/kg, p.o., 14 consecutive days, n = 7); and (xi) vorinostat (50 mg/kg, i.p., 14 consecutive days, n = 7). Only the MEK inhibitors, cobimetinib and trametinib, regressed tumor growth, and they were more significantly effective than other therapies ($p < 0.0001$, respectively), thereby demonstrating the precision of the PDOX models of PDAC and its potential for individualizing pancreatic-cancer therapy.

Plasmacytoma

The 2003 International Myeloma Working Group in classified plasmacytomas as solitary plasmacytoma of bone (SBP) when a single bone lesion was present, solitary extramedullary plasmacytoma (SEP)

when a solitary soft-tissue lesion was present and multiple solitary plasmacytoma (MSP) when multiple sites of disease were present in soft tissue, bone or both. SBP, SEP and MSP are rare clinical entities, characterised by a monoclonal plasma cell infiltrate in bone or soft tissue. Although plasmacyotoma are cytologycally and immunophenotypically identical to multiple myeloma, they are differentiated from the latter by the lack of hypercalcaemia, renal failure, anaemia, pathological monoclonal plasmocytosis on bone biopsy, bone lytic changes (except for the primary solitary lesion) and serum or urinary monoclonal protein (Dattolo 2013).

Mele and Pastore (2018) noted that extra-medullary dissemination (EMD) of myeloma usually occurs several years after diagnosis and is associated with a very poor overall survival (OS) of less than 6 months due to the fact that there are no efficient therapeutic options. In relapsed/refractory multiple myeloma (rrMM) with EMDs, the most effective treatment is a lymphoma-like polychemotherapy regimen such as PACE, Dexa-BEAM, and HyperCVAD followed by autologous peripheral blood stem cell transplant (ASCT) or allogeneic SCT. Radiotherapy (RT) of soft-tissue plasmacytoma is the further treatment choice and resulted in a high rate of local control and a prolonged disease-free survival (DFS). These investigators report the case of a 41-year old man affected by ultra-high-risk symptomatic IgAλ MM with extra-medullary intra-cranial soft-tissue relapsed after VTD-PACE followed by ASCT. The salvage program with KRd regimen (carfilzomib on days 1 to 2, 8 to 9, and 15 to 16 (starting dose 20 mg/m2 on days 1 and 2 of cycle 1, target dose 27 mg/m2 thereafter); lenalidomide 25 mg on days 1 to 21; oral dexamethasone 40 mg before each dose of carfilzomib, on days 1, 8, 15, and 22 of a 28-day cycle). The authors concluded that in this case report, the patient obtained a reduction in size of the extra-medullary intra-cranial soft-tissue even in the absence of local aggressive RT suggesting that carfilzomib and lenalidomide together could be effective also in this rare and critical situation. Moreover, these researchers stated that more clinical studies and more long-term follow-up are needed to establish the role of combined regimen KRd in the control of EMDs.

Soft Tissue Sarcoma

Nair and colleagues (2017) noted that selinexor, a small molecule that inhibits nuclear export protein XPO1, has demonstrated efficacy in solid tumors and hematologic malignancies with the evidence of clinical activity in sarcoma as a single agent. Treatment options available are very few, and hence the need to identify novel targets and strategic therapies is of utmost importance. The mechanistic effects of selinexor in sarcomas as a monotherapy and in combination with proteasome inhibitor, carfilzomib, across a panel of cell lines in-vitro and few in xenograft mouse models were investigated. Selinexor induced IκB nuclear localization as a single agent, and the effect was enhanced by stabilization of IκB when pre-treated with carfilzomib. This stabilization and retention of IκB in the nucleus resulted in inhibition of NFκB and transcriptional suppression of the critical anti-apoptotic protein, survivin. Treatment of carfilzomib followed by selinexor caused selinexor-sensitive and selinexor-resistant cell lines to be more sensitive to selinexor as determined by an increase in apoptosis. This was successfully demonstrated in the MPNST xenograft model with enhanced tumor suppression. The authors concluded that the subcellular distributions of IκB and NFκB are indicative of carcinogenesis. Inhibition of XPO1 results in intra-nuclear retention of IκB, which inhibits NFκB and thereby provides a novel mechanism for drug therapy in sarcoma. This effect can be further enhanced in relatively selinexor-resistant sarcoma cell lines by pre-treatment with the proteasome inhibitor carfilzomib. These researchers stated that because of these results, a human clinical trial with selinexor in combination with a proteasome inhibitor is planned for the treatment of sarcoma.

Jeitany and colleagues (2020) stated that proteasome inhibitors, such as bortezomib and carfilzomib, have shown efficacy in anti-cancer therapy in hematological diseases but not in solid cancers. These researchers found that liposarcomas (LPS) are susceptible to proteasome inhibition, and identified drugs that synergize with carfilzomib, such as selinexor, an inhibitor of XPO1-mediated nuclear export. Through quantitative nuclear protein profiling and phospho-kinase arrays, these researchers identified potential mode of actions of this combination, including interference with ribosome biogenesis and inhibition of pro-survival kinase PRAS40. Furthermore, by assessing global protein levels changes, FADS2, a key enzyme regulating fatty acids synthesis, was found down-regulated after proteasome inhibition. Interestingly, SC26196, an inhibitor of FADS2, synergized with carfilzomib. Finally, to identify further combinational

options, these investigators performed high-throughput drug screening and uncovered novel drug interactions with carfilzomib. For instance, cyclosporin A, a known immunosuppressive agent, enhanced carfilzomib's efficacy in-vitro and in-vivo. Altogether, these results demonstrated that carfilzomib and its combinations could be re-purposed for LPS clinical management.

Systemic Lupus Erythematosus

In a lupus-prone mice model, Ichikawa et al (2012) investigated the hypothesis that proteasome inhibition may have potential in the treatment of systemic lupus erythematosus, by targeting plasmacytoid dendritic cells (PDCs) and plasma cells, both of which are critical in disease pathogenesis. The authors concluded that inhibition of the immunoproteasome is equally efficacious as dual targeting agents in preventing lupus disease progression by targeting 2 critical pathways in disease pathogenesis, type I IFN activation and autoantibody production by plasma cells.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
Other CPT codes related to the CPB:	
96365 - 96368	Intravenous infusion
96379	Unlisted therapeutic, prophylactic, or diagnostic intravenous or intra-arterial injection or infusion
96409	Chemotherapy administration; intravenous, push technique, single or initial substance/drug
HCPCS codes covered if selection criteria are met:	
J9047	Injection, carfilzomib, 1 mg
Other HCPCS codes related to the CPB:	
Thalidomide - no specific code	
J1094	Injection, dexamethasone acetate, 1 mg
J1100	Injection, dexamethasone sodium phosphate, 1 mg

Code	Code Description
J8530	Cyclophosphamide, oral, 25 mg
J8540	Dexamethasone, oral, 0.25 mg
J9041	Injection, bortezomib, 0.1 mg
J9145	Injection, daratumumab, 10 mg
J9070	Cyclophosphamide, 100 mg
J9227	Injection, isatuximab-irfc, 10 mg
J9312	Injection, rituximab, 10 mg
ICD-10 codes covered if selection criteria are met:	
C83.00 - C83.09, C83.30 - C83.39, C83.80 - C83.99	Non-follicular lymphoma
C88.0 - C88.9	Malignant immunoproliferative diseases and certain other B-cell lymphomas [for transplant candidates with progressive solitary plasmacytoma]
C90.00 - C90.02	Multiple myeloma
C90.10	Plasma cell leukemia not having achieved remission
C90.12	Plasma cell leukemia in relapse
ICD-10 codes not covered for indications listed in the CPB (not all inclusive) :	
C00.0 - C14.8	Malignant neoplasm of lip, oral cavity and pharynx
C15.3 - C15.9	Malignant neoplasm of esophagus
C25.0 - C25.9	Pancreatic cancer
C40.00 - C41.9	Malignant neoplasm of bone [osteosarcoma]
C49.0 - C49.9	Malignant neoplasm of connective and soft tissue [soft tissue sarcoma]
C50.011 - C50.929	Breast cancer
C56.1 - C56.9	Malignant neoplasm of ovary
C71.0 - C71.9	Malignant neoplasm of brain [glioblastoma]

Code	Code Description
C74.00 - C74.92	Malignant neoplasm of adrenal gland [neuroblastoma]
C76.0	Malignant neoplasm of head, face and neck
C83.10 - C83.19	Mantle cell lymphoma
C85.10 - C85.99	Non-Hodgkin lymphoma
C90.30 - C90.32	Solitary plasmacytoma
I67.82	Cerebral ischemia [ischemic brain injury]
G90.1	Familial dysautonomia [Riley-Day]
M32.0 - M32.9	Systemic lupus erythematosus
T86.810	Lung transplant rejection

The above policy is based on the following references:

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