Carfilzomib

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U. M. Martens (ed.), *Small Molecules in Hematology*, Recent Results in Cancer Research 211, https://doi.org/10.1007/978-3-319-91439-8_13

Abstract

Carfilzomib (CFZ) is a potent, second-generation proteasome inhibitor (PI), with significant activity as a single agent and in combination with other antimyeloma agents in patients with relapsed or refractory multiple myeloma (RRMM). CFZ binds selectively and irreversibly to its target and leads to antiproliferative and proapoptotic effects on cancer cells. This irreversible inhibition is dose- and time-dependent in vitro and in vivo. CFZ as monotherapy and in combination with other antimyeloma agents (e.g., as CFZ and dexamethasone [Kd]) achieved very good responses, progression-free survival (PFS) and overall survival (OS). In several ongoing studies, CFZ is being investigated in triplet and quadruplet schedules of CFZ, lenalidomide and dexamethasone (KRd), CFZ, cyclophosphamide, dexamethasone (KCd) and with antibodies, like elotuzumab or daratumumab. The multitude of completed and ongoing studies confirmed a tolerable safety profile of CFZ, a significantly lower incidence of neuropathy compared to bortezomib (BTZ) and a slightly higher incidence of cardiotoxicity, which is closely observed and precautions taken to avoid them as best as possible. In July 2012, the US Food and Drug Administration (FDA) approved CFZ as a single agent for RRMM patients with disease progression after two prior therapies, including BTZ and immunomodulatory drugs (IMiDs). The combination of KRd and Kd followed, being approved by both FDA and European Medicines Agency (EMA) in 2015 and 2016, respectively. Moreover, CFZ is being evaluated in patients with newly diagnosed MM (NDMM), in high-risk smoldering MM and for maintenance approaches.

Keywords

Novel proteasome inhibitor · Irreversible · Carfilzomib · Relapsed/refractory disease · Multiple myeloma

1 Introduction

Multiple myeloma (MM) is characterized by proliferation of monoclonal plasma cells (PCs) in the bone marrow (BM) and accounts for approximately 10% of hematological malignancies (Rajkumar and Kumar 2016). The treatment of MM has substantially changed in the last decade due to the introduction of novel agents (NA) with new specific target structures against malignant cells. Among immunomodulatory drugs (IMiD), novel immunotherapies, including antibodies and various others (such as histone deacetylase inhibitors [HDACi]), proteasome inhibitors (PIs) play a pivotal role in the treatment of MM today.

Proteasomes are present in all eukaryotic cells. They degrade proteins and influence multiple cellular processes, including proliferation and DNA repair, so that their inhibition leads to cell cycle arrest and apoptosis. Unique immunoproteasomes exist in cells of immune or hematopoietic origin, where the catalytic sites differ from the constitutive proteasomes. Both constitutive and immunoproteasomes are expressed in MM cells and are targeted by PIs (Kortuem and Stewart 2013).

After the introduction of the first PI bortezomib (BTZ/V), second- and third-generation PIs have been developed, aiming to be potentially more efficacious and less toxic, including an improved polyneuropathy (PNP) side effect profile. Carfilzomib (CFZ/K) is a potent, selective, and irreversible second-generation PI, which granted approval for the treatment of relapsed/refractory MM (RRMM). The US Food and Drug Administration (FDA) approved CFZ monotherapy in RRMM patients in 2012. Moreover, the combination of CFZ, lenalidomide and dexamethasone (KRd) and CFZ and dexamethasone (Kd) followed, being approved by both FDA and European Medicines Agency (EMA) in 2015 and 2016, respectively.

In several clinical studies, CFZ has shown substantial antitumor activity in hematological malignancies, while exhibiting a well-tolerated side effect profile: The ENDEAVOR study compared Kd versus BTZ plus dexamethasone (Vd) and determined a longer progression-free survival (PFS) and lower risk of painful PNP with Kd (Dimopoulos et al. 2016). In the ASPIRE study, superiority of KRd vs. Rd, with unprecedented PFS differences in RRMM, was shown, and study results have recently been updated (Stewart et al. 2017). However, cardiac toxicity has been observed in a small proportion of patients, leading to the determination of potential risks and precautions that have been defined as relevant to observe to prudently use CFZ (Rajkumar and Kumar 2016). CFZ guideline papers are under way to guide these decisions and to conduct best surveillance and co-medication in different CFZ regimens (S. Bringhen, personal communication, 2018).

2 Structure and Mechanism of Action

CFZ, formerly known as PR-171 (Khan and Stewart 2011; Stewart 2012), is a PI that irreversibly interacts with the proteasome (Khan and Stewart 2011). Since it belongs to the epoxyketone-based PIs, CFZ is structurally and functionally distinct from BTZ (Khan and Stewart 2011; Demo et al. 2007). Due to the irreversible binding of CFZ, the response is more sustained than with the reversible BTZ (Demo et al. 2007) and the proteasome activity is decreased to less than 20%. Only by a new synthesis of the proteasome subunits and a new compilation it is possible to restore this irreversible binding (Kuhn et al. 2007). This CFZ property leads to minimal off-target inhibition to other proteases (Khan and Stewart 2011).

The proteasome itself is a multicatalytic protease complex (Fig. 1), that is responsible for the ubiquitin-dependent turnover of cellular proteins (Ciechanover 2005; Dalton 2004; Kisselev and Goldberg 2001). The inhibition of the proteasome leads to an accumulation of proteins in the cell guiding the cell into apoptosis (Adams 2004). Two units form the 26S proteasome, the 19S and the 20S units. This 20S unit consists of four stacked rings, two α-rings and two β-rings, of each seven subunits (α_1–α_7; β_1–β_7). The inner two β-subunit rings encode for three major catalytic activities, the caspase-like (C-L) proteolytic activity (β_1), the trypsin-like (T-L) (β_2), and the chymotrypsin-like (CT-L) proteolytic activity (β_7) (Kisselev and

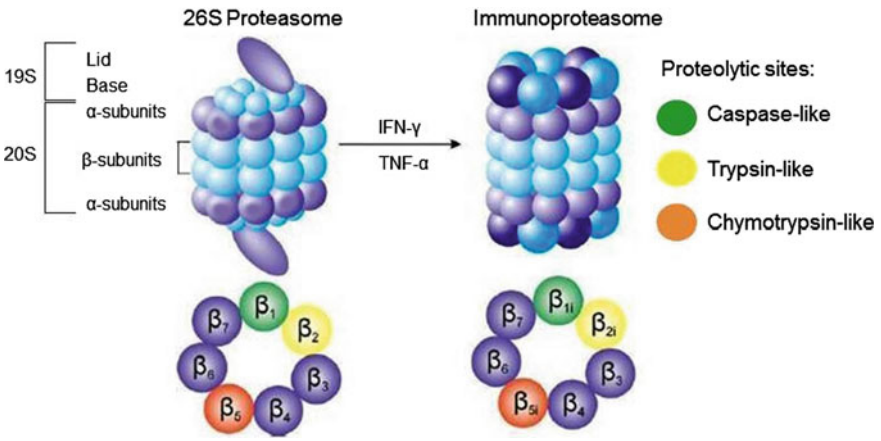

Fig. 1 Structure of the 26S proteasome and immunoproteasome with the three different catalytic sites. In cells from hematopoietic origin different factors like interferon (IFN)-γ and tumor necrosis factor (TNF)-α lead to the synthesis of the immunoproteasome. The arrangement of the three different catalytic sites is displayed between the proteasome and the immunoproteasome. Adapted from Kubiczkova et al. (2014), Kisselev and Goldberg (2001), Ciechanover (2005)

Goldberg 2005; Kuhn et al. 2009). Hematologically derived tumor cells express a variant 20S core, the i20S, making it an ideal target for PIs in the treatment of hematological cancers (Parlati et al. 2009). Since the CT-L activity is the rate limiting step of the proteolysis, it is the primary target for this drug class (Rock et al. 1994). The approval of BTZ led to the validation of the ubiquitin–proteasome pathway as a target for cancer therapy (Demo et al. 2007).

The epoxyketone-based CFZ is a potent and highly selective inhibitor of the CT-L catalytic subunit of the i20S proteasome or so-called immunoproteasome (Kuhn et al. 2007; O'Connor et al. 2009). The inhibition has an antiproliferative and proapoptotic effect on the cancer cell. The high selectivity of CFZ eliminates the potential off-target activity with other cellular proteases (Demo et al. 2007; Kuhn et al. 2007; Parlati et al. 2009). The epoxyketone structure (Fig. 2) leads to this

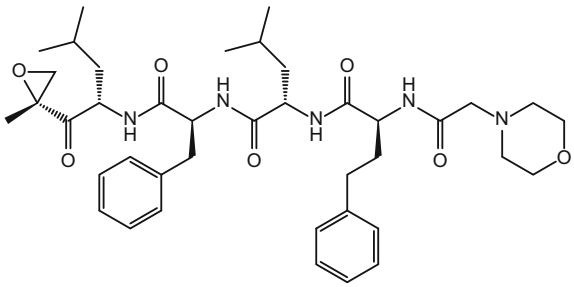

Fig. 2 Chemical structure of carfilzomib, an epoxyketone-based irreversible proteasome inhibitor (Kubiczkova et al. 2014)

Table 1 Characteristics and key features of carfilzomib

Pharmacodynamics			
Active moiety	Proteasome target	Key cellular effects	Binding
Tetrapeptide epoxyketone	CT-L subunit	Caspase-3, 7, 8, 9; JNK, eIF2, NOXA	Irreversible (N-terminal to threonine)
Application notes			
Dosage	Half-life (min)	Application	
20–56 mg/m^2	<30	Intravenous	

CT-L—*c*hymotrypsin-like, *eIF2*—eukaryotic Initiation Factor 2, *JNK*—c-Jun N-terminal *kinase*, *NOXA* PMAIP1—phorbol-12-myristate-13-acetate-induced protein 1, *mg*—milligram; *m*—meter
Adapted from Kuhn et al. (2007), Tsakiri et al. (2013), Kubiczkova et al. (2014)

special characteristic of CFZ, due to the specificity of the NH_2-terminal threonine residue of the kinase ending in the inhibition of the enzyme activity (Kuhn et al. 2007).

By binding to the proteasome, CFZ forms a unique six-atom ring structure with the β_5-subunit that leads to an intramolecular cyclization and morpholino adduction (Kisselev and Goldberg 2001; Ruschak et al. 2011). This process is a two-step mechanism composed of the nucleophilic attack of the oxygen from the hydroxyl group of threonine 1 (Thr1) to carbon of the epoxyketone leading to the formation of a hemiacetal. In the second steps, the α-amino nitrogen of Thr1 nucleophilically attacks the C_2 carbon–epoxide ring, as a result this forms the morpholine adduct (Kisselev and Goldberg 2001; Ruschak et al. 2011).

The blockage of the proteasome induces several external and internal apoptotic cascades in the cell, like the elevation of the Caspases-3, 7, 8, 9. Additionally, the activation of c-Jun N-terminal kinase (JNK), the mitochondrial membrane depolarization, and a cytochrome c release is associated with programmed cell death. Furthermore, the accumulation of non-functional proteins and an increased level of NOXA induce ER stress connected with a decreased level of phosphorylated eukaryotic initiation factor 2 (eIF2) (Kuhn et al. 2007; Parlati et al. 2009). CFZ also promotes mesenchymal stem cell (MSC) differentiation into osteoclasts, similar to BTZ (Hu et al. 2013).

With no increased toxicity, CFZ can induce apoptosis in BTZ-naïve and pretreated MM cells (Demo et al. 2007; Kuhn et al. 2007). Other mechanisms are also important for the toxicity of PIs, like dissociation half-life, pharmacokinetic, and pharmacodynamics (Table 1). Since CFZ as an epoxyketone PI has a significantly milder impact on the neuromusculatory system, this has been postulated as one reason for CFZ's lower neurotoxicity (Tsakiri et al. 2013).

3 Preclinical Data

The most exclusively expressed mammalian cytosolic 26S proteasome consists of two regulatory 19S cap subunits and one 20S core particle including two outer α-rings and two inner β-rings with three catalytically active sites (chymotrypsin-, trypsin-, and caspase-like proteolytic sites). Hence, the proteasomal ubiquitin-dependent proteolysis plays a crucial role in cellular homeostasis, particularly in excessively paraprotein-expressing MM cells (Kisselev et al. 2012). The epoxyketone class PI CFZ is a potent and highly selective, covalent inhibitor of the chymotrypsin-like (CT-L) activity within the 20S core subunit (Khan and Stewart 2011), leads to cellular protein accumulation and finally induces apoptosis. Moreover, CFZ demonstrated to overcome BTZ resistance in MM patient-derived cell culture models and worked synergistically in combination with dexamethasone in vitro (Kuhn et al. 2007). Additionally, CFZ, different to BTZ, can overcome BM stroma protection by inhibiting phosphorylated C-X-C chemokine receptor type 4 (pCXCR-4) and can cause downregulation of the cell surface marker CD138 in myeloma cells in vitro (Waldschmidt et al. 2017). In mice and monkeys, two consecutive intravenous (IV) boluses within 24 h (e.g., 1, 2; 8, 9; 15, 16; of a 28-day cycle) could demonstrate reduction of tumor growth and did cumulatively inhibit proteasomal activity, while a once-weekly schedule allowed proteasome recovery (Demo et al. 2007).

4 Clinical Data

CFZ is a second-generation PI that received approval for the treatment of RRMM patients, who have received at least two prior therapies, including BTZ and one IMiD. CFZ is active as a single agent and in combination with others antimyeloma agents.

4.1 Relapsed and Refractory MM (RRMM)

4.1.1 Single-Agent CFZ—Phase I/II Studies

The efficacy of CFZ in heavily pretreated, RRMM has been evaluated in a number of phase II trials. PX-171-003 was a multicenter, open-label, single-arm, phase II study. This registration trial led to FDA approval of CFZ in RRMM: 266 patients with prior exposure to BTZ and IMiDs were enrolled in this study. The median number of prior therapy lines was 5. CFZ was administered IV two consecutive days each week for three weeks in the 28-day treatment cycle. Patient received 20 mg/m^2 at a daily dose in cycle 1, and 27 mg/m^2 in subsequent cycles, until disease progression, unacceptable toxicity, or for a maximum of 12 cycles. The overall response rate (ORR) was 23.7%, with a median duration of response of

7.8 months. PFS and OS in response evaluable patients ($n = 257$) were 3.7 and 15.6 months, respectively. The therapy was generally well tolerated; 190 patients discontinued treatment due to progressive disease (59%) or AEs (12%). Dose reduction due to adverse events (AEs) was required in 17.7%. Drug-related AEs of all grades were most frequently fatigue (37%), nausea (3%), and thrombocytopenia (Jagannath et al. 2012; Siegel et al. 2012).

Vij et al. performed other clinical CFZ trials: The PX-171-004 trial enrolled 129 BTZ-naïve patients and 35 patients with prior BTZ treatment. In the first phase of the trial, CFZ was administrated in cohort 1 (94 patients) with 20 mg/m^2 IV on days 1, 2, 8, 9, 15, 16, every 28 days for up to 12 cycles. In the second phase of the study, 67 patients who tolerated 20 mg/m^2 CFZ during cycle 1 received an escalated dose of 27 mg/m^2 beginning in cycle 2. ORR in the BTZ-naïve cohort was 47.6%, while in the BTZ-pretreated cohort was 17.1%. In the BTZ-naïve cohort, the clinical benefit rate (CBR) was 61.9% after 6 CFZ-cycles (Vij et al. 2012b); whereas in BTZ-pretreated patients 31.4%. The median duration of response (DOR) was >10.6 months (Vij et al. 2012a). No differences in tolerability between both cohorts were observed. The most common reported AEs were non-hematological and included fatigue, nausea, dyspnea, which were primarily $\leq$ grade 2. Grade 3/4 events were less common and included thrombocytopenia, neutropenia, and lymphopenia, while PNP was rarely observed. No dose modification was required in patients with baseline renal function impairment. Both PX-171-003 and PX-171-004 studies demonstrated that CFZ was tolerable and active in RRMM, suggested a more rewarding activity in patients with lesser pretreatment (as has been univocally shown for other antimyeloma agents) and the PX-171-004 trial confirmed a dose–response relationship with single-agent CFZ (20 vs. 27 mg/m^2) (Jakubowiak 2014).

The open-label, multicenter phase II study PX-171-005 was designed to assess the influence of renal impairment (RI) on CFZ's pharmacokinetics (PK) in RRMM. Badros et al. (2013) enrolled 50 patients with varying degrees of renal function, ranging from normal to long-term dialysis patients. Patients received CFZ via IV infusion over 2–10 min on days 1, 2, 8, 9, 15, 16 of 28-day cycles for up to 12 cycles. The starting dose was 15 mg/m^2 in cycle 1. If tolerated, the CFZ dose was increased to 20 mg/m^2 in cycle 2 and to 27 mg/m^2 in cycle 3 and subsequent cycles. The results demonstrated a similar duration of drug exposure and clearance regardless of renal function with a similar rate of proteasomal ChT-L activity inhibition. Toxicities were similar between groups, and the incidence of AEs was independent of renal status. No dose modification was required. Therefore, CFZ was proposed as an appropriate treatment also in patients with severe RI, albeit admittedly, this phase II trial was small, which limits the general applicability of this subgroup analysis.

4.1.2 CFZ in Combination with Dexamethasone (Kd)—Phase I/II Study

In 2016, Berenson et al. presented results of the phase I/II, multicenter, single-arm, dose-escalation CHAMPION-1 study. This was the first clinical trial, which

evaluated the safety and efficacy of once-weekly Kd in RRMM. CFZ was administered as a 30-min IV infusion on days 1, 8, and 15 of a 28-day cycle: 27 patients were enrolled in the phase I, dose-escalation study and received CFZ at 20 mg/m^2 on cycle 1 day 1. Subsequent doses were escalated in a standard 3 + 3 dose-escalation schema to 45, 56, 70, or 88 mg/m^2, to determine the maximum tolerated dose (MTD). In the phase 2 portion, 89 patients received CFZ at the MTD of the same schedule as in the phase 1 portion. All patients received additional dexamethasone with 40 mg (IV or orally) on days 1, 8, 15, and 22 for the first 8 cycles, whereas this was omitted on day 22 from cycle 9 and onward. Investigators observed no dose-limiting toxicities (DLT) across the 45, 56, and 70 mg/m^2 cohorts. The MTD of CFZ was therefore determined as 70 mg/m^2. The median PFS in 104 patients treated with the MTD was 12.6 months, the ORR was 77%, and 48 patients achieved $\geq$ VGPR. The frequency of any grade and $\geq$ grade 3 AEs was similar or lower than those reported in the Kd group of the phase III ENDEAVOR study (Berenson et al. 2016). This regime is evaluated in the phase III ARROW study, which compares the efficacy and safety of once-weekly 20/70 mg/m^2 Kd versus twice-weekly 20/27 mg/m^2 Kd in RRMM.

4.1.3 CFZ in Combination with Immunomodulatory Drugs (IMiDs)—Phase Ib/II Study

In June 2008, Wang et al. started the phase Ib/II study PX-171-006 to evaluate CFZ in combination with standard-dose lenalidomide (25 mg/d, days 1–21) and low-dose dexamethasone (40 mg once weekly) (KRd) in RRMM. CFZ was initiated at 15 mg/m^2 and was escalated to a maximal dose of 27 mg/m^2: 84 patients were treated in 28-day cycles; of those 62% within the maximum planned dose (MPD) cohort. The ORR was 69% and median PFS was 11.8 months. ORR, duration of response (DOR), and PFS in the MPD cohort were even better with 76.9%, 22.1, and 15.4 months, respectively. The AEs led to dose reduction in 7.7% and to treatment discontinuation in 19.2% of patients. Frequent hematological AEs of any grade were lymphopenia, neutropenia, and anemia, and common non-hematological AEs like fatigue and diarrhea. Grade 3/4 events were generally hematological and included lymphopenia (48.1%), neutropenia (32.7%), thrombocytopenia (19.2%), and anemia (19.2%) (Wang et al. 2013a). Results of this trial demonstrated that KRd was well tolerated and highly active in RRMM.

Therefore, Shah et al. (2015) designed an open-label, multicenter, phase I study of CFZ, pomalidomide, and dexamethasone. All 32 patients had been refractory to prior lenalidomide, and almost all were also BTZ-refractory. They received CFZ 20/27 mg/m^2 over 30 min on days 1, 2, 8, 9, 15, 16, pomalidomide 4 mg once daily on days 1–21 and dexamethasone 40 mg on days 1, 8, 15, and 22, every 28 days for the first 6 cycles. After termination of 6 cycles, maintenance therapy with CFZ on days 1, 2, 15, and 16 and pomalidomide on days 1–21 was continued. Patients received a median of 7 cycles. The ORR was 50% and the median PFS 7.2 months. Maintenance in cycle 7 was performed in 17 patients. Of the 32 enrolled patients, 8 required dose reduction and 7 treatment discontinuation due to AEs.

4.1.4 CFZ in Combination with Cyclophosphamide and Dexamethasone (KCd)—Phase II Study

Yong et al. (2017) presented at the American Society of Hematology Meeting 2017 results of the phase II MUK *five* study. The aim of this study was to compare the activity and safety of 6 cycles of CFZ versus 8 cycle of BTZ in triplet combination with cyclophosphamide and dexamethasone (KCd vs. VCd). A total of 300 patients at first relapse, or refractory to no more than 1 previous line of therapy, were randomized, 201 to KCd and 99 to VCd group. Participants in the KCd arm received CFZ 20/36 mg/m^2 biweekly (weeks 1–3) as IV infusion in the 28-day cycle, in the VCd arm BTZ 1.3 mg/m^2 was administered biweekly (weeks 1 and 2) subcutaneously in 21-day cycles. Both groups received cyclophosphamide 500 mg and dexamethasone 40 mg orally weekly. Patients in the KCd group with at least stable disease after 6 cycles of therapy were randomized to receive maintenance CFZ or no further treatment, patients in the VCd group did not receive maintenance. In the KCd arm, 81.6% of patients received all 6 treatment cycles, versus 53.5% with 8 completed cycles in the VCd arm. KCd group achieved significant higher major response ($\geq$ VGPR) at 24 weeks (40.2 vs. 31.9% for VCd). The OS for KCd and VCd was 84 and 68.1%, respectively. Treatment emergent neuropathy occurred more often in the VCd arm (56.3 vs. 21.4% with KCd). The incidence of $\geq$ grade 3 neuropathy or $\geq$ grade 2 neuropathy with pain was lower in the KCd group (1.5 vs. 19.8% with VCd). Cardiac SAEs were reported in 4.2% of patients in the KCd arm (vs. 1.4% VCd arm), neurological SAEs occurred more frequently in the VCd arm (8.1 vs. 0.7%). The results of this study showed that patients in the KCd arm achieved better OS, the regimen was generally well tolerated, and the incidence of neuropathy was significant lower than in the VCd arm.

4.1.5 Phase III CFZ Combination Trials: KRd (ASPIRE), KD (ENDEAVOR), and CFZ Alone (FOCUS)

Due to the promising results of KRd in phase I and II trials, Stewart et al. started a randomized, open-label, multicenter, phase III study in July 2010, which led to FDA approval of KRd in RRMM. This ASPIRE study was designed to compare the combination of KRd versus Rd. The investigators enrolled 792 RRMM patients who had previously received 1–3 prior lines, the median being 2 in both groups, with 66% having received prior BTZ- and 20% R-regimens. CFZ was administrated as a 10-min infusion on days 1, 2, 8, 9, 15, and 16 of cycles 1–12 (starting dose 20 mg/m^2 on days 1 and 2 of cycle 1 and 27 mg/m^2 thereafter) and on days 1, 2, 15, and 16 during cycles 13 through 18. Patients in both groups received 25 mg lenalidomide on days 1–21 and 40 mg dexamethasone on days 1, 8, 15, and 22 of a 28-days cycle until disease progression. The primary study endpoint was PFS in the intent-to-treat population. Secondary endpoints included OS, ORR, DOR, quality of life, and safety. The KRd group demonstrated significantly longer PFS (median 26.3 months) compared to Rd (17.6 months). The median OS was also shown to be improved (Stewart et al. 2017). The ORR was 87.1% with KRd versus 66.7% with Rd, including CRs or better in 31.8 versus 9.3%, respectively. The median DOR with KRd versus Rd was 28.6 versus 21.2 months, respectively. KRd-patient in

the <70-year age subgroup reported improved health-related quality of life (HRQOL) in comparison to the Rd control group. No significant differences were observed between the KRd and Rd groups in the >70-year age subgroup (Stewart et al. 2016). Over 18 months, the global health status/quality of life (GHS-QoL) was greater in patients in the KRd than those in the Rd arm. Patients in the KRd group experienced a longer time to GHS/QoL deterioration than the Rd group, with the median time to deterioration (≥ 5 points) of 10.3 versus 4.8 months, respectively. Dyspnea (2.8 vs. 1.8%), cardiac failure (3.8 vs. 1.8%), ischemic heart disease (3.3 vs. 2.1%), hypertension (4.3 vs. 1.8%), and acute renal failure (3.3 vs. 3.1%) occurred more often with KRd. There was no difference between KRd und Rd groups in the incidence of PNP (17.1 vs. 17%, respectively). Treatment discontinuation due to AEs appeared in 15% with KRd versus 17.7% with Rd. The findings of the ASPIRE study demonstrated that KRd resulted in significantly improved ORR, PFS, and OS in RRMM patients. KRd also showed a favorable benefit-risk profile compared with Rd, irrespective of previous treatment (Stewart et al. 2015; Dimopoulos et al. 2017b, c).

In January 2016, Dimopoulos et al. presented results of the randomized, open-label, multicenter ENDEAVOR study, which compared Kd versus Vd in RRMM patients, who had received 1–3 previous therapies. Prior treatments could include BTZ, if patients achieved at least a partial response (PR) upon PI-treatment before relapse or progression. A total of 929 patients were enrolled and stratified by previous PIs, prior lines of therapy, ISS stage, and route of BTZ delivery, if randomized to Vd. CFZ was given as a 30-min infusion on days 1, 2, 8, 9, 15, and 16 of 28-day cycles (20 mg/m^2 d1 and 2 of cycle 1; 56 mg/m^2 thereafter). BTZ was administrated as IV bolus or subcutaneously, with a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 of 21-days cycle. Patients received 20 mg dexamethasone on days 1, 2, 8, 9, 15, 16, 22, 23 in the Kd group and on days 1, 2, 4, 5, 8, 9, 11, 12 in the VD group. Patients were treated until progression, withdrawal of consent or unacceptable toxicity. In the first interim analysis, the ORR was significantly higher with Kd versus Vd (77 vs. 63%, respectively), including VGPR or better in 54% with Kd and 29% with Vd. The PFS also favored Kd versus Vd (median 18.7 vs. 9.4 months, respectively). The median DOR was 21.3 months for Kd and 10.4 months for Vd. These results translated into prolonged OS (Kd: 47.6 vs. Vd: 40 months) and suggested that therapy with the selective, irreversible PI CFZ may induce higher responses, PFS and OS in RRMM than with BTZ. Of note, significantly higher GHS-QoL was reported in the CFZ group, albeit 99% of patients in both groups had any grade AEs. The incidence of grade 2 or worsened PNP was significantly higher in the Vd than Kd group (35 vs. 7%, respectively). The most frequent $\geq$ grade 3 AEs, which led to treatment discontinuation in the Kd group were cardiac failure, decrease in ejection fraction, asthenia, and acute renal failure and with Vd PNP, fatigue, dyspnea, and diarrhea. The median time to discontinuation in the Kd group was 6.8 and 4.3 months in the Vd group. Dose reduction due to AEs was necessary in 32% of patients in the Kd group and in 50% in the Vd group. The results of the study demonstrated that Kd versus Vd led to significantly

and clinically meaningful improvements in OS, PFS, and objective response in RRMM (Dimopoulos et al. 2016, 2017a).

Hajek et al. (2012) presented results of the randomized, phase III, open-label, multicenter study FOCUS (PX-171-011), which investigated CFZ monotherapy versus low-dose corticosteroids with optional cyclophosphamide. A total of 315 patients were enrolled into this study and comprised the intent-to-treat population. The median number of 5 prior regimens was extensive. The median treatment duration was higher in the CFZ than in the control group (16.3 vs. 10.7 weeks, respectively). Median PFS in the CFZ group was 3.7 months compared with 3.3 months in the control group. Patients in the control group started next anti-myeloma therapy earlier than in the CFZ group. The median ORR in the CFZ group was 19.1 versus 11.4% in the control group. Moreover, the number of patients achieving minimal response or better was higher with CFZ than in the control population (31.2 vs. 20.8%, respectively). Incidence of treatment-related AEs was similar in both groups. Findings of this FOCUS study confirmed the safety profile of CFZ and suggested that CFZ in advanced and highly pretreated MM patients needs combination partners.

4.2 Newly Diagnosed Multiple Myeloma (NDMM)

CFZ as monotherapy and in combination with other antimyeloma agents has been investigated in newly diagnosed MM (NDMM) patients in several ongoing and completed studies:

CYKLONE is a phase Ib/II study designed to investigate CFZ in 64 transplant-eligible NDMM patients. Patients were treated with the 4-agent combination of CFZ (days 1, 2, 8, 9, 15, 16), 300 mg/m^2 cyclophosphamide (days 1, 8, 15), 100 mg thalidomide (days 1–28), and 40 mg dexamethasone (days 1, 8, 15, 22) in 28-day cycles. CFZ was dose-escalated at 4 dose levels to determine the MTD, which was 20/36 mg/m^2. Those 59% of patients treated at the MTD in the phase II part achieved a VGPR or better. In the overall population, the ORR was 91% and 44 patients achieved $\geq$VGPR. Mikheal et al. demonstrated that the CYKLONE combination led to rapid and deep responses with limited neuropathy, cardiac or pulmonary toxicity in NDMM patients (Mikhael et al. 2015).

Bringhen et al. (2014) assessed the safety and efficacy of CFZ in combination with cyclophosphamide and dexamethasone (KCd) in NDMM patients $\geq$65 years of age and ineligible for autologous stem cell transplantation (ASCT) in a multicenter, open-label phase II trial. Investigators enrolled 58 patients, who received KCd for up to 9 cycles, followed by maintenance with CFZ until progression or intolerance. Patients received oral cyclophosphamide 300 mg/m^2 and dexamethasone 40 mg on days 1, 8, and 15; CFZ (20/36 mg/m^2) was administrated as 30-min infusions on days 1, 2, 8, 9, 15, 16. In the maintenance phase, patients were treated with 36 mg/m^2 CFZ on days 1, 2, 15, 16 every 28 days. Response was prompt and showed improvement over time. After a median of 9 cycles of KCd, 71% of patients achieved $\geq$VGPR. After a median follow-up of 18 months, the 2-year

PFS and OS were 76 and 87%, respectively. The rate of $\geq$ grade 3 AEs was low, and the most common toxicities were neutropenia (20%), anemia (11%), and cardiopulmonary events (7%). This KCd regime showed a good safety profile and high efficacy with prominent CR rates, also in elderly patients.

Bringhen and colleague also presented results of weekly CFZ, combined with cyclophosphamide and dexamethasone. Patients were treated with CFZ on days 1, 8, and 15 of a 28-day cycle. A total of 63 patients were enrolled in the phase I and phase II of the study, 54 of them received recommended phase 2 dose 70 mg/m^2. At least very good PR was achieved in 36 (66%) of these 54 patients. The frequency of hematological and non-hematological AEs was similar to, or lower, than reported in previous study with twice-weekly CFZ (Bringhen et al. 2017).

Currently, a comparative trial of KRd versus KCD in younger patients, eligible for ASCT, is being performed by the GIMEMA (Italian) study group, preliminary results suggesting similar efficacy and toxicity for both induction schedules (Gay et al. 2017).

Several triplet and quadruplet schedules of KRD, KCD, e.g., with both antibodies elotuzumab and daratumumab, are being assessed in phase II/III clinical trials (e.g., DSMM; GMMG). The results of these studies are eagerly expected.

5 Toxicity

Most common side effects of CFZ reported in trials have been anemia, dyspnea, diarrhea, nausea, and fatigue. In the comparative analysis of 4 sequential phase II trials (PX-171-003-A0, PX-171-003-A1, PX-171-004, and PX-171-005) in 526 patients receiving single-agent CFZ at doses ranging from 15 to 27 mg/m^2, most common hematological toxicities (grade $\geq$ 3) were thrombocytopenia (23.4%), anemia (22.4%), lymphopenia (18.1%), and neutropenia (10.3%). Non-hematological toxicities were generally grade 1/2, although grade 3/4 grade toxicities did include pneumonia (10.5%), cardiac failure (9.5%), fatigue (7.6%), and RI (7.2%) (Harvey 2014; Muchtar et al. 2016). CFZ may bear the risk of cardiac toxicity, predominantly in patients with pre-existing cardiac impairment. Probably it is a direct result of reduced proteasome activity in the cardiac myocytes (Li and Wang 2011). Cardiovascular events were likewise reported in BTZ patients. Thus, this effect was particularly compared in the ENDEAVOR study, which demonstrated a higher frequency of any cardiac events of any grade in the Kd versus Vd group (12 vs. 4%). The most commonly reported cardiovascular events were new onset or worsening congestive heart failure, arrhythmia (mostly of low grade), myocardial infarction, pulmonary hypertension, sudden cardiac death, and an asymptomatic decrease in left ventricular ejection fraction (LVEF). Echocardiography, cardiac magnetic resonance imaging (MRI), or longer term blood pressure monitoring are recommended in patients with risk factors for cardiac

events. Patients who developed cardiac toxicity should be regularly monitored regarding blood pressure, LVEF, heart rate, cardiac ischemia, dyspnea, and volume overload.

Infusion-related reactions (IRR) occurred following CFZ administration in >10% of patients. Within the first 24–48 h of CFZ application, IRR were reported and characterized by a constellation of symptoms, including fever, rigor, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, dyspnea, hypotension, syncope, chest tightness, and angina. IRR under CFZ may be prevented or allayed with dexamethasone prophylaxis. The toxicity profile of CFZ is intensively investigated in many phase I, II, and III studies. CFZ is generally considered well-tolerated, with a manageable toxicity profile for most patients (Table 2).

Table 2 Management of adverse events (AEs) in MM patients receiving CFZ

Toxicity	Recommended action
Hematological toxicity Neutropenia (grade 3/4) Thrombocytopenia (grade 4)	• Withhold dose • If fully recovered before next scheduled dose, continue at same dose level • Thrombocytopenia: If the patient recovers to grade 3 thrombocytopenia, reduce dose by one dose level • Neutropenia: If the patient recovers to grade 2 neutropenia, reduce dose by one dose level • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician
Cardiac toxicity Grade 3 or 4, new onset or worsening of • congestive heart failure • decreased left ventricular function • or myocardial ischemia	• Withhold until resolved or returned to baseline, stop fluid administration • After resolution, consider restarting CFZ at 1 dose level reduction (KRd: 27 mg/m^2→20 mg/m^2→15 mg/m^2, Kd: 56 mg/m^2→45 mg/m^2 36 mg/m^2→27 mg/m^2) based on a benefit/risk assessment • Resuming therapy: Follow-up EKG and biomarker monitoring (BNP or NT-pro-BNP) are recommended • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician
Pulmonary hypertension or *Peripheral neuropathy (grad 3/4)*	• Withhold until resolved or returned to baseline • Restart at the dose used prior to the event or reduced dose at the discretion of the physicians • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician
Pulmonary complications (grade 3/4) or *Other grade 3/4 non-hematological toxicities*	• Withhold until resolved or returned to baseline • Consider restarting at the next scheduled treatment with one dose level reduction • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician

(continued)

Table 2 (continued)

Toxicity	Recommended action
Hepatic toxicity *Grade 3/4 elevation of transaminases, bilirubin or other liver abnormalities*	• Withhold until resolved or returned to baseline • After resolution, consider if restarting CFZ is appropriate • If appropriate, reinitiate at the reduced dose with frequent monitoring of liver function • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician
Renal toxicity *Serum creatinine* $\geq$ *2x baseline*	• Withhold until renal function has recovered to Grade 1 or to baseline and monitor renal function • If attributable to CFZ, restart at the next scheduled treatment at a reduced dose • If not attributable to CFZ, restart at the dose used prior to the event • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician

Adapted from Harvey (2014), Ludwig et al. (2017)

6 Drug Interactions

CFZ is characterized by a high systemic clearance and a short half-life period in patients with solid tumors ($t_{1/2}$). It is mainly metabolized via peptidase cleavage and epoxide hydrolysis (Yang et al. 2011). In vitro studies demonstrated that CFZ did not induce effects on human CYP 1A2 and CYP 3A4 in cultured fresh human hepatocytes. Cytochrome P450-mediated metabolism plays a marginal role in elimination of CFZ. The open-label, phase I, non-randomized, clinical drug interaction study enrolled 18 patients with solid tumors: 17 of them received at least 1 dose of CFZ and 67% (n = 12) completed a full cycle of administration. Repeated administration of CFZ (on day 1 + 16) did not result in significant interactions with midazolam via pharmacokinetics. The results of this study demonstrate that CFZ can be administered with other medications that are substrates of CYP3A4 (Wang et al. 2013b). It is unknown if CFZ is an inducer of CYP1A2, 2C8, 2C9, 2C19, and 2B6. Caution should be observed when combined with products which are substrates of these enzymes, including oral contraceptives (Onyx Pharmaceuticals 2012).

7 Biomarkers

Valid biomarkers that are predictive of response to therapy, survival and AEs are clinically relevant. Bhutani et al. showed that CXCR4 modulation after one day of CFZ monotherapy was predictive of early clinical response to KRd. Patients who

responded to CFZ at 24 h with a decrease or no change in CXCR4 expression in PCs showed early clinical response in cycles 1–3 compared to those who had an increase in CXCR4 expression (Bhutani et al. 2014). Moreover, an increased expression of tight junction protein (TJP1) could be observed during the adaptive response mediating CFZ resistance in the LP-1/CFZ cell line (Riz and Hawley 2017). A strong association between higher immunoglobulin expression and sensitivity of CFZ was noted. Combined IGH and Fc gamma receptor 2B (FCGR2B) expression constitutes a retrospective validated biomarker that classifies CFZ response with 70% sensitivity and 94% specificity (Tuch et al. 2014). Also the difference between involved and uninvolved serum heavy-light chains (HLC) after 2 cycles of KRd was suggested as an independent predictor of early CR, as well as minimal residual disease (MRD) among high-risk smoldering myeloma (SMM) and NDMM patients treated with KRd. Normalization of the HLC ratio after 2 cycles of KRd appeared significantly associated with obtained nCR/CR/sCR (Bhutani et al. 2013). The 19S proteasome levels were predictive of response and survival. In patients receiving combination therapy with KRd, higher pretreatment 19S proteasome levels correlated with deeper clinical response to treatment. Additionally, higher pretreatment proteasome levels were predictive of improved duration of response and PFS (Korde et al. 2014). Furthermore, Jonsson et al. (2015) suggested early change in tumor size based on M-protein modeling as an early biomarker for survival in MM following exposure to single-agent CFZ. Four circulating micro-RNAs (miRNAs) were identified to be related to different PFS in patients treated with KRd. MiR-103a and miR-199 were associated with deceased risk of PFS, whereas miR-278 and miR-99 were associated with increased risk for progression. Cardiovascular events are known complications to CFZ and eagerly explored to be predicted in MM patients. Matrix metalloproteinase-1 (MMP-1) has been suggested as a potential biomarker for patients at risk for cardiovascular events when treated with CFZ. MM patients who developed cardiovascular events had 37% lower MMP-1 compared to those without (Lendvai et al. 2015). Albeit these biomarkers are further explored, their routine clinical use is inapt (Table 3).

Table 3 Biomarkers for response, PFS/OS, and cardiovascular events

Response	PFS/OS	CV events
19S proteasome levels	ECTS	MMP-1
CXCR4 modulation	miRNAs (miR-99, -199, -103a, and -378)	
TJP-1		
IGH & FCGR2B-expression		
HLC		

PFS—progression-free survival, *OS*—overall survival, *CV*—cardiovascular, *CXCR4*—CXC-chemokine receptor type 4, *TJP-1*—tight junction protein-1, *IGH*—immunoglobulin heavy chain, *FCGR2B*—low-affinity immunoglobulin gamma Fc region receptor II-b, *HLC*—serum heavy-light chain, *ECTS*—early change in tumor size, *miRNA*—microRNA, *RNA*—ribonucleic acid, *MMP-1*—matrix metalloproteinase-1

8 Summary and Perspective

CFZ is a potent PI and important component of antimyeloma treatment in a variety of regimens, including Kd, KRd, and KCd. CFZ has also been investigated with other IMiDs, such as pomalidomide and thalidomide, with different alkylators (e.g., CFZ-Bendamustine-Dex) and antibodies like daratumumab or elotuzumab in clinical trials. Due to its substantial efficacy and good tolerability, it is used in doublet, triplet, and quadruplet combinations, both in younger and older, ASCT-eligible and -ineligible patients. CFZ is considered a potent relapse option in MM patients who have relapsed after and/or are refractory to both BTZ and IMiD. The findings from ongoing phase II and multiple phase III studies will help to determine optional dosing regimens and to establish the position of CFZ in relapse, first- and subsequent-line therapy and maintenance approaches in even more depth in the near future.

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