Treatment With Carfilzomib: A Promising Future for Multiple Myeloma

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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Abstract

The survival outlook for patients with multiple myeloma (MM) has improved over the past decade; however, even with access to newer therapies, all patients will eventually relapse and progress. Carfilzomib is a selective proteasome inhibitor and a promising MM treatment that was approved by the US Food and Drug Administration (FDA) in 2012. This review will highlight the future of carfilzomib by summarizing how the agent is being investigated in ongoing clinical trials. While standard carfilzomib (FDA-approved dose and schedule) is effective for MM treatment, clinical trials are investigating alternate dosing schemes of carfilzomib, including higher doses with longer infusion times and altered dosing schedules. Additionally, combination studies are elucidating important treatment options, both for patients who have relapsed and refractory MM and for patients who are newly diagnosed with MM. Drug combinations with carfilzomib have the potential to offer novel treatment options and improved overall survival. Finally, ongoing phase III randomized studies with carfilzomib will establish a broader representation of the many potential capabilities of the drug. The results of these trials will help to further define the role of carfilzomib in MM therapy, which may help to provide patients with improved overall survival and quality of life.

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The outlook for patients with multiple myeloma (MM) has changed dramatically over the past decade, with the advent of new therapies that have led to improved survival rates (Kastritis et al., 2009; Kumar et al., 2008; Lonial, Mitsiades, & Richardson, 2011). Unfortunately, even with access to newer therapies, all patients will eventually relapse and progress (Kumar et al., 2012; Laubach et al., 2011). Treatment-related toxicities remain a concern. Advances in MM treatment will require regimens that balance efficacy and safety, and sequential regimens may be necessary (Mohty et

al., 2012; van de Donk et al., 2011). The treatment of patients with relapsed and refractory MM (RR MM) is particularly challenging due to a combination of the disease itself and side effects of various treatments (Laubach et al., 2011; van de Donk et al., 2011).

With the advent of bortezomib (Velcade), the proteasome became a validated target in myeloma management, and combinations with other agents have proven successful in myeloma management (Nooka et al., 2013). Carfilzomib (Kyprolis) was granted accelerated approval by the US Food and Drug Administration (FDA) in 2012 for the treatment of patients with MM who have received at least two prior therapies, including bortezomib and an immunomodulatory drug (IMiD), and who have demonstrated disease progression on or within 60 days of completion of last therapy (Onyx Pharmaceuticals, 2012).

Single-agent carfilzomib, administered intravenously (IV) over 2 to 10 minutes at doses up to 27 mg/m^2 (standard carfilzomib, i.e., the FDA-approved dose) has proven to be effective for patients with RR MM (Badros et al., 2013; Jagannath et al., 2012; Siegel et al., 2012; Vij et al., 2012a, 2012b). Carfilzomib is being investigated as a single agent when infused over a longer time, allowing for administration of higher doses, as well as in combination with other MM treatments in patients with both RR MM and newly diagnosed MM. This review summarizes the findings from these trials that aim to help define the present and future role of carfilzomib in the armamentarium of MM treatment. An overview of ongoing carfilzomib trials is illustrated in Table 1.

ALTERNATIVE DOSES AND SCHEDULES

While a dose of 20/27 mg/m^2 of single-agent carfilzomib is effective in treating RR MM, alternate dosing schedules are being explored. Early clinical data suggested a carfilzomib dose response in a multivariate modeling analysis (Squifflet et al., 2011). Additionally, preclinical data showed lower maximum concentration (C_{max}), equivalent proteasome inhibition, and reduced toxicity with longer infusion times of carfilzomib (Yang et al., 2011). These data led to testing a 30-minute infusion of carfilzomib in order to administer higher carfilzomib doses. PX-171-007 (referred to here as 007, NCT00531284) and NCT01351623 are single-agent, 30-minute infusion studies in patients with RR MM treated with carfilzomib from which promising response rates have been reported (Table 2).

The 007 study established a maximum tolerated dose (MTD) of 56 mg/m^2, at which dose there was an overall response rate (ORR) of 60% (Papadopoulos et al., 2011). The majority of adverse events (AEs) at this dose were grade 1 and 2 with the exception of thrombocytopenia, anemia, and hypertension (grade ≥ 3 in 38%, 21%, and 13% of patients, respectively), and 21% of patients required a dose reduction. In the other 30-minute single-agent infusion study, ORR in patients who completed four cycles of therapy was 58% (50% in the overall population) and median progression-free survival (PFS) was 4.6 months (Lendvai et al., 2012). The most common treatment-related, nonhematologic grade 3/4 AEs included hypertension (21%), lung infection (18%), and pulmonary edema (9%), and 35% of patients required a dose reduction.

Additional ongoing studies investigating a higher dose of carfilzomib through longer infusion times include CARAMEL 2 (NCT01812720), which is investigating a 30-minute carfilzomib infusion following stem cell transplantation, and a phase I/II study (NCT01792102) investigating a 60-minute infusion of carfilzomib 56 mg/m^2. Alternate dosing schedules are also being investigated. The CHAMPION-1 study (NCT01677858), which is currently recruiting patients, is specifically investigating once-weekly dosing of carfilzomib.

COMBINATION STUDIES

Due to the heterogeneity of MM, combination therapy has been demonstrated as an important treatment option. Many studies are under way investigating combinations with carfilzomib in patients with RR MM (Table 3) and newly diagnosed MM (Table 4).

Combinations in Patients With Relapsed or Relapsed Refractory MM

Treatment for patients with RR MM is complicated because the treatment depends on both disease-related factors, i.e., quality and duration of response to other treatments, aggressiveness of the disease, and patient-related factors, i.e., preexisting toxicity from previous therapy, age, performance status, and comorbidities (Mohty et al.,

Table 1. Ongoing Carfilzomib Trials

Registration number	Study name and description	Phase	Treatment arms	Status (primary completion date)
Single-agent relapsed and/or refractory MM				
NCT00531284	PX-171-007; 30-min infusion	Ib/II	Carfilzomib	Active, not recruiting (1/14)
NCT00884312	PX-171-010; extension protocol	II	Carfilzomib	Active, not recruiting (4/14)
NCT01302392	PX-171-011; FOCUS	III	Carfilzomib vs. best supportive care	Active, not recruiting (6/14)
NCT01351623	Carfilzomib (30-min infusion)	II	Carfilzomib 56 mg/m^2	Active, not recruiting (5/13)
NCT01775553	High-dose carfilzomib; CAR-IST-534	II	Carfilzomib 56 mg/m^2	Not yet recruiting (8/16)
Single agent + dexamethasone				
NCT00531284	PX-171-007; 30-min infusion	Ib/II	Carfilzomib + dexamethasone	Active, not recruiting (1/14)
NCT01568866	ENDEAVOR; 30-min infusion	III	Carfilzomib + dexamethasone vs. bortezomib + dexamethasone	Recruiting (1/15)
NCT01677858	Weekly carfilzomib + dexamethasone; 30-min infusion	I/II	Carfilzomib + dexamethasone	Recruiting (7/14)
NCT01812720	Treatment following stem cell transplant (CARAMEL 2); 30-min infusion	II	Carfilzomib + dexamethasone	Not yet recruiting (9/14)
NCT01792102	60-min infusion of carfilzomib; IST-CAR-585	I/II	Carfilzomib + dexamethasone	Not yet recruiting (3/15)
Relapsed and/or refractory (combinations)				
NCT00603447	PX-171-006	I/II	Carfilzomib with lenalidomide + dexamethasone	Active, not recruiting (8/13)
NCT01365559	Treatment of bortezomib-RR MM; IST-CAR-516	I/II	Carfilzomib + non-IMiD regimen drug vs. carfilzomib + IMiD-containing regimen	Recruiting (12/12)
NCT01372540	Safety and efficacy with ARRY-520	I	ARRY-520 + carfilzomib	Recruiting (2/15)
NCT01301807	Dose escalation of carfilzomib + panobinostat	I	Carfilzomib + panobinostat	Recruiting (8/15)
NCT01496118	Safety and efficacy with panobinostat	I/II	Carfilzomib + panobinostat	Recruiting (12/13)
NCT01549431	Combination effects of carfilzomib + panobinostat	I	Carfilzomib + panobinostat	Recruiting (1/14)
NCT01246063	Safety and efficacy with PLD	I/II	Carfilzomib + PLD	Recruiting (7/14)
NCT01464034	Dose finding with pomalidomide; IST-CAR-521	I	Carfilzomib, pomalidomide, dexamethasone	Recruiting (10/13)
NCT01665794	Dose finding with pomalidomide	I/II	Carfilzomib + pomalidomide + dexamethasone	Recruiting (8/14)
NCT01080391	PX-171-009; ASPIRE	III	Carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone	Active, not recruiting (12/13)

Note. MM = multiple myeloma; RR = relapsed/refractory; IMiD = immunomodulatory drug; PLD = pegylated liposomal doxorubicin; G-CSF = granulocyte colony-stimulating factor; NA = not applicable; CRd = carfilzomib, lenalidomide, and dexamethasone; CCyTd = carfilzomib, cyclophosphamide, thalidomide, and dexamethasone; CCd = carfilzomib, cyclophosphamide, and dexamethasone; CTd = carfilzomib, thalidomide, and dexamethasone.

Table 1. Ongoing Carfilzomib Trials (cont.)

Registration number	Study name and description	Phase	Treatment arms	Status (primary completion date)
Relapsed and/or refractory (combinations)				
NCT01297764	QUAD RV-0549	I/II	Vorinostat + lenalidomide + carfilzomib + dexamethasone	Recruiting (12/13)
NCT01690143	Conditioning study; IST-CAR-536	I/II	Carfilzomib + high-dose melphalan	Recruiting (11/14)
NCT01537861	G-CSF + carfilzomib		Filgrastim + carfilzomib or bortezomib	Recruiting (7/13)
NCT00999414	Compassionate use; UARK 2009-32	NA	Carfilzomib	Active, not recruiting (12/13)
First-line combinations				
NCT01029054	CRd	I/II	Carfilzomib + lenalidomide + dexamethasone	Active, not recruiting (6/14)
NCT01057225	CYCLONE (CCyTd)	I/II	Carfilzomib + cyclophosphamide + thalidomide + dexamethasone	Recruiting (1/15)
NCT01279694	CARMYSAP (elderly patients)	I/II	Carfilzomib + melphalan + prednisone	Recruiting (9/12)
NCT01346787	CCd; IST-CAR-506	II	Carfilzomib + cyclophosphamide + dexamethasone	Recruiting (7/12)
NCT01402284	CRd	II	Carfilzomib + lenalidomide + dexamethasone	Recruiting; (9/15)
NCT01559935	Car-BiRD (sequential treatment)	II	Carfilzomib + clarithromycin + lenalidomide + dexamethasone	Recruiting (3/14)
NCT01660750	11-MM-01; CAR-IST-520	I	Carfilzomib + cyclophosphamide + dexamethasone	Recruiting (9/13)
NTR2422; EUCTR2009-014922-40-NL	CARTHADEX (CTd)	I/II	Carfilzomib + thalidomide + dexamethasone	Ongoing, not recruiting
NCT01816971	CRd before and after stem cell transplant	II	Carfilzomib + lenalidomide + dexamethasone	Recruiting (12/14)
NCT01818752	CLARION	III	Carfilzomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone	Recruiting (4/16)
Related therapeutic areas				
NCT01572480	Smoldering MM	II	Carfilzomib + lenalidomide + dexamethasone	Recruiting (4/16)
NCT01658904	Plasma cell myeloma	I/II	Carfilzomib + melphalan + filgrastim	Recruiting (6/17)
NCT01813227	Waldenström macroglobulinemia; Pro 3596 (IST-CAR-531)	II	Carfilzomib + rituximab + dexamethasone	Not yet recruiting (4/15)
NCT01789242	Light chain amyloidosis; IST-CAR-545	I	Carfilzomib + dexamethasone	Recruiting (8/14)

Note. MM = multiple myeloma; RR = relapsed/refractory; IMiD = immunomodulatory drug; PLD = pegylated liposomal doxorubicin; G-CSF = granulocyte colony-stimulating factor; NA = not applicable; CRd = carfilzomib, lenalidomide, and dexamethasone; CCyTd = carfilzomib, cyclophosphamide, thalidomid, and dexamethasone; CCd = carfilzomib, cyclophosphamide, and dexamethasone; CTd = carfilzomib, thalidomide, and dexamethasone.

Table 2. Alternative Infusion and Dosing Studies With Available Data (Carfilzomib as a Single Agent or With Low-Dose Dexamethasone)

Study	Patients (N, response evaluable)	Regimen	Efficacy	Implications
PX-171-007, NCT00531284 (Papadopoulos et al., 2011)	RR MM (24)	30-min infusion, 56 mg/m^2	60% ORR; 1 sCR, 4 VGPR, 7 PR	A 30-min infusion of carfilzomib (± dexamethasone) allows for higher doses of carfilzomib to be administered with higher responses and comparable toxicity
NCT01351623 (Lendvai et al., 2012)	RR MM (34)	30-min infusion, 56 mg/m^2	58% ORR; 1 CR, 7 VGPR, 6 PR	
007 Cd, NCT00531284 (Badros et al., 2012)	RR MM (20)	30-min infusion, 45 or 56 mg/m^2 + 40 mg/wk dexamethasone	55%; 2 VGPR, 9 PR	

Note. RR MM = relapsed/refractory multiple myeloma; ORR = objective response rate; sCR = stringent complete response; VGPR = very good partial response; PR = partial response; CR = complete response; Cd = carfilzomib plus dexamethasone.

2012). Patients at high risk for disease are generally treated with combination regimens for maximal response (Laubach et al., 2011).

Current studies have reported promising results when combining carfilzomib with IMiDs lenalidomide (Revlimid) or pomalidomide (Pomalyst). PX-171-006 (NCT00603447) investigated the combination of carfilzomib with lenalidomide and dexamethasone in a phase Ib (Niesvizky et al., 2013a) and phase II (Niesvizky et al., 2013b) trial of patients with relapsed or progressive MM. In the 40 patients evaluable for response across the dose-escalation groups (phase Ib, in which the carfilzomib doses ranged from 15 to 27 mg/m^2), the ORR was 62.5% with a duration of response (DOR) for patients with ≥ partial response (PR) of 11.8 months and overall PFS of 10.2 months (Niesvizky et al., 2013a). The combination had a tolerable safety profile, and the MTD was not reached. Therefore, the maximum planned dose (MPD) of 27 mg/m^2 was expanded in the phase II portion in 52 patients in whom an ORR of 76.9% was reported with a median PFS of 15.4 months (Niesvizky et al., 2013b). The treatment was well tolerated with discontinuations due to an AE reported for 15% of patients.

Trials NCT01665794 and NCT01464034 (Stadtmauer et al., 2013) are dose-finding studies combining carfilzomib with pomalidomide. Results are available from the latter study in which an MTD of 20/27 mg/m^2 carfilzomib, 4 mg pomalidomide, and 40 mg dexamethasone was established and an ORR of 50% was reached (Stadtmauer et al., 2013). The combination was well tolerated with limited grade 3/4 toxicities.

Additionally, three studies combining the histone deacetylase (HDAC) inhibitor panobinostat with carfilzomib are in progress (NCT01496118, NCT01301807, and NCT01549431); preliminary results demonstrate promising response rates with a tolerable safety profile and no unexpected toxicities and merit the investigation of higher doses (Berdeja et al., 2012; Kaufman et al., 2013; Shah et al., 2012a). QUAD (NCT01297764) is a four-drug combination of carfilzomib, lenalidomide, the HDAC inhibitor vorinostat (Zolinza), and dexamethasone designed to determine the MTD and safety/tolerability of the combination. No dose-limiting toxicities (DLTs) have yet been reported at the current combination of carfilzomib 20/27 mg/m^2, lenalidomide 25 mg, vorinostat 300 mg, and dexamethasone 40 mg, with a promising preliminary response rate and manageable safety profile (Bilotti et al., 2013).

When carfilzomib was combined with ARRY-520 (NCT01372540), a novel kinesin spindle protein inhibitor (Shah et al., 2012b), the combination was well tolerated and showed signs of activity. Updated results report accrual ongoing at the final cohort of full-dose ARRY-520 of 1.5 mg/m^2 and 20/27 mg/m^2 carfilzomib with 1 DLT in that cohort and 9/17 patients overall still on the study, with no patients discontinuing therapy due to toxicity (Shah et al., 2013). Other combination studies with no reported results to date include combination with pegylated liposomal doxorubicin (NCT01246063), a carfilzomib conditioning study with high-dose melphalan (NCT01690143), and a bone marrow study combining filgrastim plus carfilzomib or bortezomib (NCT01537861).

Table 3. Combination Studies in Relapsed or Relapsed/Refractory Multiple Myeloma

Study	N	Carfilzomib dose	Additional regimen	Efficacy	Conclusion or implications
PX-171-006, NCT00603447, phase Ib (Niesvizky et al., 2013a)	40	15–27 mg/m² IV over 2–10 min	Lenalidomide 10–25 mg/day (days 1–21); dexamethasone 40 mg/wk	62.5% ORR; 1 sCR, 13 VGPR, 11 PR	Combinations with IMiDs are feasible and encourage ongoing investigation
PX-171-006, NCT00603447, phase II (Niesvizky et al., 2013b)	52	20/27 mg/m² IV over 2–10 min	Lenalidomide 25 mg/day (days 1–21); dexamethasone 40 mg/wk	76.9% ORR; 2 sCR (median follow-up 24.4 mo)	
Dose finding with pomalidomide, NCT01464034 (Stadtmauer et al., 2013)	30	27 mg/m² IV over 30 min	Pomalidomide 4 mg/day, dexamethasone 40 mg/wk	50% ORR; 4 VGPR, 11 PR	
Panobinostat dose escalation, NCT01496118 (Berdeja et al., 2012)	10	< 27 mg/m² IV over 10 min; 27, 36, and 45 mg/m² IV over 30 min	Panobinostat 20 mg 3×/wk, each week 1 and 3	50% ORR; 1 VGPR, 4 PR	Promising early efficacy encourages higher dose escalation
Panobinostat dose escalation, NCT01301807 (Shah et al., 2012)	20	20/27–45 mg/m² IV over 30 min	Panobinostat 20 mg 3×/wk	(n = 17) 35% ORR; 2 VGPR, 4 PR	Promising response rate in heavily pretreated patients
Panobinostat combination, NCT01549431 (Kaufman et al., 2013)	10	20/27 mg/m² to 20/56 mg/m² over 30 min for doses > 27 mg/m²	Panobinostat 15–25 mg 3×/wk	ORR 30%; 1 sCR, 2 PR	Promising response and toxicity profile of the combination at the current dose of carfilzomib 20/36 mg/m² and panobinostat 20 mg
QUAD, NCT01297764 (Bilotti et al., 2013)	15	15, 20, or 20/27 mg/m²	Lenalidomide 15 or 25 mg (days 1–21), vorinostat 300 or 400 mg (days 1–7, 15–21), dexamethasone 40 mg/wk	(n = 11) ORR 40%; 4 PR	Combination is well tolerated with no dose-limiting toxicities identified to this point
Car-ARRY, NCT01372540 (Shah et al., 2012)	8	20/27 mg/m² IV over 30 min	0.75–1.0 mg/m² (days 1, 2, 15, 16) ARRY-520	(n = 6) ORR 16.7%; 1 nCR	Early signals of activity show combinations with novel agents are promising
Car-ARRY expansion (Shah et al., 2013)	17	20/27 mg/m² IV over 30 min	0.75–1.5 mg/m² (days 1, 2, 15, 16) ARRY-520	NR	Combination is well-tolerated with limited hematologic toxicity
IST-CAR-516, NCT01365559 (Berenson et al., 2013)	37	20–45 mg/m² IV over 30 min	Prior bortezomib-containing regimen (13 different combinations)	(n = 33); 45.5% ORR; 2 CR, 6 VGPR, 7 PR	Carfilzomib is an effective and tolerable replacement for bortezomib
Compassionate use; UARK 2009-32, NCT00999414 (Usmani et al., 2011)	81	27 or 36 mg/m²	Additional anti-MM drugs added cycle 2 onward in absence of PR	5% nCR, CR, or sCR	Worsening or new PN not observed in the majority of patients; promising combinations observed (+ dexamethasone + lenalidomide + vorinostat in particular)

Note. IV = intravenous; ORR = objective response rate; sCR = stringent complete response; VGPR = very good partial response; PR = partial response; IMiD = immunomodulatory drug; nCR = near complete response; NR = not reported; MM = multiple myeloma; PN = peripheral neuropathy.

Table 4. First-Line Combination Studies With Carfilzomib

Study	N	Carfilzomib dose	Additional agents	Efficacy	Conclusion or implications
CRd, NCT01029054 (Jakubowiak et al., 2012)	53	20 or 27 mg/m² IV over 5–10 min; 36 mg/m² IV over 30 min	Lenalidomide 25 mg/day (days 1–21); dexamethasone 40 mg or 20 mg/wk	98% ORR; 22 sCR, 11 nCR, 10 VGPR, 9 PR (median 13-mo follow-up)	CRd is a highly potent and tolerable combination regimen in patients with newly diagnosed MM; it is now a recommended Category 2A regimen for primary treatment in transplant-eligible patients
CRd, NCT01029054 (Jakubowiak et al., 2013)	53	20 or 27 mg/m² IV over 5–10 min; 36 mg/m² IV over 30 min	Lenalidomide 25 mg/day (days 1–21); dexamethasone 40 mg or 20 mg/wk	98% ORR, 87% ≥ VGPR, 72% ≥ nCR, 53% ≥ sCR (median 25-mo follow-up)	
CRd, NCT01029054 subset of elderly patients in the study aged ≥ 65 years (Jakubowiak et al., 2013)	23	20 or 27 mg/m² IV over 5–10 min; 36 mg/m² IV over 30 min	Lenalidomide 25 mg/day (days 1–21); dexamethasone 40 mg or 20 mg/wk	100% ORR; 87% ≥ VGPR	
CRd, NCT01402284 (Korde et al., 2013)	31	20/36 mg/m² IV	Lenalidomide 25 mg/day (days 1–21); dexamethasone 40 mg or 20 mg/wk	(n = 28) 96.4% ORR; 11 sCR, 7 nCR, 4 VGPR, 5 PR	
CARTHADEX, NTR2422 (Sonneveld et al., 2012)	58	27 or 36 mg/m² (induction and consolidation)	Thalidomide 200 mg/day + dexamethasone 40 mg/wk (induction) Thalidomide 50 mg/day + dexamethasone 20 mg/wk (consolidation)	Carfilzomib 27 mg/m² cohort (n = 40) Induction: 88% ORR with 18% ≥ CR; Consolidation: 90% ORR with 35% ≥ CR	Carfilzomib is rapidly effective when combined with thalidomide and response can be enhanced with consolidation therapy
CYCLONE, NCT01057225 (Mikhael et al., 2012)	38	15–45 mg/m² IV	Cyclophosphamide 300 mg/m²/wk, thalidomide 100 mg/day, + dexamethasone 40 mg/wk	(n = 27); 96% ORR; 29% CR, 46% VGPR, 21% PR	Four-drug combinations containing carfilzomib are highly efficacious and tolerable
CARMYSAP (CMP), NCT01279694 (Moreau et al., 2013)	69	27–45 mg/m² IV in 42-day cycles for 9 cycles	After 9 cycles, combined with melphalan 9 mg/m² + prednisone 60 mg/m² days 1–4	89% ORR; 51% > VGPR	Carfilzomib combination with melphalan compares favorably to other melphalan combinations
CCd, NCT01346787 (Bringhen et al., 2013)	58	20/36 mg/m² IV	Cyclophosphamide 300 mg/m²/wk + dexamethasone 40 mg/wk (+ carfilzomib for 9 cycles) followed by maintenance with carfilzomib	(n = 41); 93% ORR; 12% ≥ sCR, 46% ≥ CR/nCR, 68% ≥ VGPR (median follow-up of 8 mo)	Encouraging activity with CCd with limited need for dose reduction

Note. CRd = carfilzomib, lenalidomide, and low-dose dexamethasone; ORR = objective response rate; sCR = stringent complete response; nCR = near complete response; VGPR = very good partial response; PR = partial response; MM = multiple myeloma; CR = complete response; CMP = carfilzomib plus melphalan-prednisone; CCd = carfilzomib, cyclophosphamide, and dexamethasone

Some studies are investigating carfilzomib in multiple combinations simultaneously. Bortezomib has been replaced with carfilzomib in a phase I/II study in bortezomib-refractory patients who had received bortezomib in a combination regimen with or without an IMiD agent (NCT01365559; Berenson et al., 2012). Updated results for this study indicate that an MTD has been reached for

at least one regimen (carfilzomib 45 mg/m^2 plus ascorbic acid plus cyclophosphamide), and clinical benefit was seen in 70% of patients with 6% complete response (CR) and 18% very good partial response (VGPR; Berenson et al., 2013). The combinations are well tolerated with the most common grade ≥ 3 AEs being all hematologic, including lymphopenia (35%), thrombocytopenia (19%), neutropenia (11%), and anemia (8%). Efficacy with various combinations also was seen in the carfilzomib compassionate use program UARK 2009-32 (NCT00999414), where anti-MM drugs were added to carfilzomib in cycle 2 in the absence of a PR, resulting in the identification of combinations with encouraging activity (Usmani et al., 2011).

Combinations in Patients With Newly Diagnosed MM

Although carfilzomib is currently approved for patients with RR MM, several studies using carfilzomib in the up-front setting suggest the use of carfilzomib in first-line MM treatment. A phase I/II study combined carfilzomib with lenalidomide and dexamethasone in patients with newly diagnosed MM eligible or ineligible for transplant (CRd, NCT01029054; Jakubowiak et al., 2012). Updated results of this study after a median of 22 cycles show an ORR of 98%, ≥ VGPR of 87% with a 24-month PFS of 94%, and overall survival (OS) at 98%; extended treatment continued to be well-tolerated (Jakubowiak et al., 2013a). In a subset of patients aged ≥ 65 years (n = 23), an ORR of 100% and ≥ VGPR of 87% were reported with AEs rates comparable to overall data with trends of higher thrombocytopenia, neutropenia, and hyperglycemia (Jakubowiak et al., 2013b).

Another study of the CRd combination (NCT01402284) was unique in that transplant-eligible patients defaulted to delayed autologous stem cell transplantation (ASCT) and minimal residual disease analyses were used to determine molecular response, illustrating that CRd induces rapid and deep remissions with tolerable side effects (Korde et al., 2013). Based on the data from these 2 CRd studies, carfilzomib + lenalidomide + dexamethasone was added as a Category 2A option for primary transplant-eligible patients according to National Comprehensive Cancer Network (NCCN) guidelines (NCCN, 2013).

Carfilzomib is rapidly effective when combined with the first-generation immunomodulatory agent, thalidomide (Thalomid). CARTHADEX (NTR2422) is a phase I/II dose-escalation trial to investigate carfilzomib combined with thalidomide and dexamethasone (CTd) for induction and consolidation in transplant-eligible patients with newly diagnosed MM (Sonneveld et al., 2012). In cohort 1 (n = 40, carfilzomib 27 mg/m^2) the ORR was 88% with ≥ CR in 18% of 35 patients who completed induction and an ORR of 90% with ≥ CR in 35% of the 17 patients who completed consolidation. Results for this trial show the treatment was well tolerated with no hematologic toxicities observed and grade 3/4 nonhematologic toxicities including tumor lysis syndrome (5%), deep vein thrombosis (10%), gastrointestinal symptoms (5%), and skin rash (8%). The results also indicate response can be enhanced with consolidation treatment with carfilzomib.

Additional treatment plans include four-drug combinations, alternate carfilzomib dosing schemes, and sequential treatment. The addition of cyclophosphamide to carfilzomib, thalidomide, and dexamethasone indicates that four-drug combinations can be a useful treatment plan for carfilzomib. CYCLONE (NCT01057225) is a phase I/II trial to investigate carfilzomib combined with cyclophosphamide, thalidomide, and dexamethasone in patients with newly diagnosed MM intended to proceed to ASCT. In 27 response-evaluable patients, ORR was 96% with 29% CR, 46% VGPR, and 21% PR (Mikhael et al., 2012).

CARMYSAP (NCT01279694) is a phase I/II trial investigating the alternate dosing scheme of carfilzomib in 42-day cycles for 9 cycles followed by the combination of carfilzomib with melphalan and prednisone (CMP) in elderly patients not eligible for ASCT. An MTD of carfilzomib 20/36 mg/m^2 was reached in the initial phase, and this dose was expanded to an additional 45 patients in phase II for a total of 69 patients, which resulted in an ORR of 89% with > VGPR of 51% (Moreau et al., 2013). The combination was well tolerated without peripheral neuropathy (PN) ≥ grade 2. Additionally, carfilzomib as maintenance treatment is being investigated in a phase II study (NCT01346787) evaluating carfilzomib combined with cyclophosphamide and dexamethasone (CCd) for 9 cycles followed by carfilzomib maintenance every 28

days until progression. In 41 response-evaluable patients, the ORR was 93% with stringent CR of 12% and ≥ CR/near CR of 46%. Responses were rapid (median time to PR, 1 month; median time to CR, 2 months) and improved with the duration of treatment reaching 100% ≥ PR and 77% ≥ VGPR after 9 cycles (Bringhen et al., 2013; Palumbo et al., 2013). The combination was well tolerated with 16% patients requiring a carfilzomib dose reduction and 11% discontinuing treatment due to an AE.

Car-BiRD (NCT01559935) is a phase II study evaluating carfilzomib as a part of sequential treatment. Carfilzomib treatment is followed by clarithromycin, lenalidomide, and dexamethasone and then lenalidomide maintenance treatment. Other studies with no results reported to date include a phase I study combining carfilzomib with cyclophosphamide and dexamethasone prior to ASCT (NCT01660750) and a phase II study combining carfilzomib with lenalidomide and dexamethasone before and after ASCT (NCT01816971).

RANDOMIZED STUDIES

Randomized studies with carfilzomib will establish a more broad representation of the drug's capabilities. FOCUS (NCT01302392) is a phase III, randomized, open-label, international, multicenter study investigating standard carfilzomib vs. low-dose corticosteroids and optional cyclophosphamide in patients with RR MM (Hajek et al., 2012). The primary endpoint is OS, with findings from the study expected to facilitate potential European Medicines Agency approval. The phase II 006 trial combining carfilzomib with lenalidomide informed ASPIRE (NCT01080391), a phase III, randomized, open-label, multicenter trial of standard carfilzomib combined with lenalidomide and dexamethasone vs. lenalidomide and dexamethasone alone in patients with relapsed or progressive MM (Moreau et al., 2011).

An amendment of the 007 trial that combined 30-minute infusion of 45 or 56 mg/m^2 carfilzomib with low-dose dexamethasone led to ENDEAVOR (NCT01568866), a phase III, head-to-head trial of high-dose carfilzomib (56 mg/m^2) infused over 30 minutes combined with low-dose dexamethasone vs. standard bortezomib (1.3 mg/m^2) combined with low-dose dexamethasone in patients with relapsed or progressive MM.

CARMYSAP, combining carfilzomib with melphalan, informed CLARION (NCT01818752), a phase III multicenter, open-label, randomized study in transplant-ineligible patients with newly diagnosed MM. Carfilzomib 36 mg/m^2 is administered over 30 to 60 minutes with melphalan and prednisone compared with standard bortezomib (IV or SC) with melphalan and prednisone. These randomized phase III trials are meant to inform the wider use of carfilzomib in MM.

CONCLUSION AND FUTURE DIRECTIONS

Survival outcomes are very poor when a patient with MM develops relapsed and/or refractory disease and treatment becomes more challenging. Significant progress has been made in the management of myeloma over the past 10 years with the development of new therapies including lenalidomide and bortezomib. Carfilzomib is a selective proteasome inhibitor with significant activity in RR MM at the FDA-approved dose and schedule. Carfilzomib has demonstrated robust and durable antitumor activity with evidence of a dose-response relationship in this patient population with a well-tolerated side-effect profile characterized by low rates of PN. Data from clinical trials evaluating efficacy and safety of carfilzomib alone and in combination with other agents in various stages of disease will help define the MM treatment paradigm. Clinical trials continue to focus on single-agent, combination, consolidation, and maintenance treatment in the up-front and relapsed setting. Combination regimens are associated with higher response rates, and ongoing trials are concentrating on combinations with IMiDs (lenalidomide and pomalidomide), HDAC inhibitors (panobinostat and vorinostat), and cytotoxic therapies (PLD, melphalan, and cyclophosphamide). These drug combinations have the potential to offer additional treatment options and further improve OS.

As carfilzomib data continue to evolve and demonstrate promise, the results of ongoing phase II and multiple phase III trials will help to further define the role of carfilzomib in MM therapy and will help establish the best dose, schedule, and supportive care in these patients. When used with appropriate consideration, carfilzomib may help to provide patients with an improved overall survival and quality of life.

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Ms. Catamero has nothing to disclose. Ms. Gleason has acted as a consultant for Celgene Corporation.

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