Carfilzomib (Kyprolis®) for patients with relapsed multiple myeloma who have received one to three prior lines of therapy

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**Authors' conclusions**
Carfilzomib (Kyprolis®) is a proteasome inhibitor, indicated in patients with multiple myeloma who have received one to three prior therapies. In July 2012, the FDA initially approved carfilzomib under the provisions of accelerated approval regulations for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. According to the label approved by the FDA in July 2015, carfilzomib is now additionally indicated (in combination with lenalidomide and dexamethasone) for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of. The EMA granted orphan designation for carfilzomib for the treatment of multiple myeloma in 2008 but marketing authorisation is still outstanding. As a condition for the FDA’s accelerated approval in 2012, the manufacturer had to submit the complete analysis of the ASPIRE trial: This phase III trial was conducted in 792 patients with relapsed multiple myeloma who had received a median of 2 prior treatments. Patients of both groups received lenalidomide (25 mg, on days 1-21) and dexamethasone (40 mg, on days 1, 8, 15, 22). Patients of the intervention group additionally received carfilzomib as a 10-minute infusion on days 1, 2, 8, 9, 15 and 16 (starting dose 20 mg/m2 on days 1 and 2 of cycle 1, target dose 27 mg/m2 thereafter) during cycles 1 through 12 and on days 1, 2, 15 and 16 during cycles 13 through 18, after which carfilzomib was discontinued. Interim analyses showed a gain in PFS of 8.7 months in patients receiving carfilzomib; risk reduction for PFS was 31%. The ORR was improved in the carfilzomib group (87.1%) compared to the control group (66.7%). Patients of the carfilzomib group achieved higher rates for complete response or better (31.8% vs. 9.3%) and for very good partial response or better (69.9% vs. 40.4%). Median OS was not yet reached in either group at the time of interim analysis; the Kaplan-Meier 24-month OS rates were 73.3% in the carfilzomib group versus 65.0% in the control group.

In the carfilzomib group, health-related quality of life was improved compared to the control group. AEs of grade 3 or higher were reported from 83.7% of carfilzomib-group patients and 80.7% of control-group patients; serious AEs were reported from 59.7% (carfilzomib group) and 53.7% (control group) of patients; they occurred most commonly during cycles 1 to 6 in the carfilzomib group and in cycles > 18 in the control group. 7.7% of patients of the carfilzomib group and 8.5% of the control group died during treatment or within 30 days after they received the last dose of study treatment. Despite the promising results of the ASPIRE trial, further evidence is needed to prove the efficacy (especially regarding overall survival) and safety of carfilzomib and to determine its role for the treatment of multiple myeloma. The most efficacious and safe combination with other drugs and the optimal line of treatment for carfilzomib administration needs to be assessed. Moreover, the patient population most suitable for carfilzomib treatment needs to be evaluated. Many issues have to be resolved, not least in light of the high cost of carfilzomib therapy.

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