Carfilzomib (Kyprolis®) with daratumumab and dexamethasone for the treatment of adult patients with multiple myeloma (MM)

General information

Drug description [1]	Indication [2]
Carfilzomib is a selective PI that irreversibly binds the proteasome, eliciting antimyeloma activity through unfolded protein stress response and other mechanisms.	Carfilzomib, in combination with daratumumab and dexamethasone, with lenalidomide and dexamethasone, or with dexamethasone alone is indicated for the treatment of adult patients with MM who have received at least one prior therapy.

Current treatment [3]

- NICE guidelines recommend the use of a number of the following possible sequences of treatments for relapsed or refractory MM:
- In instances of first relapse, the guidelines recommend the use of:
  - Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib.
  - Bortezomib – only after one prior therapy and for adults who have undergone, or are unsuitable for, bone marrow transplantation.
  - Second autologous stem cell transplant.
- Subsequent relapse treatment may include:
  - Lenalidomide in combination with dexamethasone for adults who have received two or more prior therapies.
  - Ixazomib, with lenalidomide and dexamethasone, for adults who have already had two or three lines of therapy
  - Panobinostat in combination with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent
  - Pomalidomide, in combination with low-dose dexamethasone for adults at third or subsequent relapse; that is, after three previous treatments including both lenalidomide and bortezomib
- Daratumumab monotherapy for adults whose previous therapy included a PI and an immunomodulator, and whose disease progressed on the last therapy, only if they have daratumumab after 3 previous therapies.

Regulatory status

EMA [2]

Approval status for this indication: On 12 November 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Kyprolis®.

The CHMP adopted a change to an existing indication as follows:

- Carfilzomib in combination with daratumumab and dexamethasone, with lenalidomide and dexamethasone, or with dexamethasone alone is indicated for the treatment of adult patients with MM who have received at least one prior therapy.

Other indications: none

- ✓ **Orphan status**
- ✓ **Medicine under additional monitoring**
- ✓ **Accelerated assessment**[1]

FDA [4, 5]

Approval status for this indication: On 20 August 2020, the FDA approved carfilzomib and daratumumab in combination with dexamethasone for adult patients with relapsed or refractory MM who have received one to three lines of therapy. The approval was based on two studies: CANDOR & EQUULEUS.

Other indications: Carfilzomib is indicated:

- For the treatment of adult patients with relapsed or refractory MM who have received one to three lines of therapy in combination with
  - Lenalidomide and dexamethasone; or
  - Dexamethasone
- As a single agent for the treatment of patients with relapsed or refractory MM who have received one or more lines of therapy.

Costs [6]

Kyprolis® powder for solution for infusion **10 mg = € 223,17** (ex-factory price);
Kyprolis® powder for solution for infusion **30 mg = € 669.50** (ex-factory price);
Kyprolis® powder for solution for infusion **60 mg = € 1,312.00** (ex-factory price)

[1] This medicine had an accelerated assessment, meaning that it is a medicine of major interest for public health, so its timeframe for review was 150 evaluation days rather than 210.

Study characteristics & results of two pivotal trials [1, 5, 7-9]

CANDOR trial

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CANDOR NCT03158688	466	Carfilzomib twice per week at 56 mg/m² (20 mg/m² on days 1 and 2 during cycle 1), dexamethasone, and daratumumab (KdD)	Carfilzomib twice per week at 56 mg/m² (20 mg/m² on days 1 and 2 during cycle 1), and dexamethasone (Kd)	PFS by ITT	randomized, open-label, multicenter, phase 3 trial	-	Amgen	Link

Efficacy (I vs. C)[2]

Median PFS was not reached (95% CI not estimable) vs. 15.8 months (95% CI 12.1 to not estimable) HR 0.63 (95% CI 0.46–0.85; p=0.0027)
The Kaplan-Meier **18-month PFS rates** were 62% (95% CI 55.4–67.1) vs. 43% (95% CI 32.4–52.8).
PFS benefit was generally consistent across pre-specified subgroups of clinical relevance
Overall response: achieved by 84% (95% CI 79.8–88.1) vs. 75% (67.0–81.3; OR 1.925; p=0.0080)
Very good partial response or better: 69% vs. 49%
Complete response: 29% vs. 10%
Median time to first response: 1 month in both treatment groups
Median time to complete response: 8.4 vs. 7.0 months
MRD-negativity at 12 months: achieved by 18% (95% CI 13.6–22.3) vs. 4% (1.4–8.3); OR 5.8 (95% CI 2.4–14.0; p<0.0001).
Minimal residual disease negative–**complete response at 12 months**: achieved by 13% (95% CI 9.0–16.7) vs. 1% (95% CI 0.2–4.6); OR 11.3; 95% CI 2.7–47.5; p<0.0001
Median OS: not reached in either treatment group (at a median follow-up time of 17. 2 and 17. 1 months; HR for death 0.75; 95% CI 0.49–1.13, p=0.17).
Deaths by the data cutoff date: 19% vs. 23%
The Kaplan-Meier **18-month OS rates**: 80% (95% CI 74.6–84.2) vs. 74% (95% CI 65.9–81.1)

Updated efficacy outcomes from the CANDOR study with approx. 11 months of additional follow-up [10]:
OS data were not mature
Median PFS by ORCA: 28.6 months vs. 15.2 months, HR 0.59 (95%CI, 0.45-0.78)
Median PFS – **subgroups:**

- Number of prior lines of therapy:
  - 1 prior line of therapy: NE vs. 21.3 months, HR 0.66 (95%CI, 0.42-1.04)
  - ≥ 2 prior lines of therapy: 24.2 vs. 12.5 months, HR 0.55 (95%CI, 0.39-0.78)
- Refractory to proteasome inhibitor:
  - No: NE vs. 16.6 months, HR 0.58 (0.40-0.82)
  - Yes: 13.1 vs. 8.7 months, HR 0.65 (0.42-1.00)
- Prior lenalidomide exposure:
  - No: NE vs. 21.3 months, HR 0.64 (95%CI, 0.43-0.95)
  - Yes: 25.9 vs. 11.1 months, HR 0.49 (95%CI 0.33-0.74)

Safety (I vs. C, safety population)[3]

All-grade TEAEs: n=306/308 (99%) vs. n=147/153 (96%)
Grade ≥3 AEs: n=253/308 (82%) vs. 113/153 (74%)
SAEs: n=173/308 (56%) vs. n=70/153 (46%)
Fatal TEAEs: n=30/308 (10%) vs. n=8/153 (5%)
Treatment-related deaths: n=5[4] (2%) vs. n=0 (0%)
Discontinuation[5]: n=69/308 (22%) vs. n=38/153 (25%)

Updated safety [10]:
Grade ≥3 AEs: 87.0% vs. 75.8%
Fatal AEs (excludes patients listed with a reason of plasma cell myeloma): 8.8% vs. 4.6%
AEs leading to carfilzomib treatment discontinuation: 26.0 vs. 22.2%

[2] CANDOR trial primary analysis data; the trial is ongoing until 07/2022
[3] CANDOR trial primary analysis data; the trial is ongoing until 07/2022
[4] pneumonia; sepsis with development of Clostridium difficile enterocolitis; septic shock in the setting of pneumocystis pneumonia; Acinetobacter infection; and cardiorespiratory arrest
[5] discontinuation due to AE(s)

- ❖ Refractory to lenalidomide
  - No: 28.6 vs. 19.9 months, HR 0.63 (95%CI, 0.44-0.90)
  - Yes: 28.1 vs. 11.1 months, HR 0.46 (95%CI, 0.28-0.73)
- ❖ 1 prior line of therapy:
  - Prior lenalidomide exposure: 25.0 vs 11.1, HR 0.38 (95%CI, 0.15-0.97)
  - Refractory to lenalidomide: 25.0 vs. 9.3 months, HR 0.11 (95%CI, 0.02-0.52)
  - Lenalidomide naïve: NE vs. NE, HR 0.75 (95% CI, 0.44-1.30)
- ❖ ≥ 2 prior lines of therapy:
  - Prior lenalidomide exposure: 28.1 vs. 12.0 months, HR 0.52 (95%CI, 0.33-0.82)
  - Refractory to lenalidomide: 28.1 vs. 12.0 months, HR 0.52 (95%CI, 0.32-0.86)
  - Lenalidomide naïve: 22.6 vs. 15.8 months, HR 0.53 (95%CI, 0.30-0.94)

EQUULEUS trial

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
EQUULEUS, MMY 1001 NCT01998971	85	Daratumumab + Carfilzomib (weekly on days 1, 8, and 15 of each 28-day cycle; 20 mg/m² initial dose, escalated to 70 mg/m² thereafter) + Dexamethasone (D-Kd)	-	Safety and tolerability of D-Kd	open-label, non-randomized, multicenter, multiarm, phase 1b study	-	Janssen Research & Development, LLC	Link

Efficacy (I vs. C)

ORR (bortezomib-refractory patients): 84%, including 20% of patients achieving CR or better; **ORR** (lenalidomide-refractory patients): 79%; **ORR** (patients with high-risk features): 69%; **ORR** (standard-risk patients): 90%
MRD-negative rate (n=4): 36%
Median PFS: was not reached in the all treated population; **12-month PFS rate**: 74%; **18-month PFS rate**: 66%
Median OS had not been reached in the all treated population (at a median follow-up of 16.6 months); **the 12-month OS rate** was 82%.
Median OS also had not been reached for the lenalidomide-refractory and PI/IMiD-refractory subgroups, with **12-month OS rates** of 75% for both groups; **the 12-month OS rate** for bortezomib-refractory patients was 76%.

Safety (I vs. C)

Any grade TEAEs: n=85/85 (100%)
Grade 3/4 TEAEs: n=65/85 (77%)
Serious TEAEs: n=38/85 (45%)[6]
Death[7]: n=3 (3.5%)
Discontinuation[8]: n=5/85 (5%)

Risk of bias (study level): CANDOR trial

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	no	no, open-label	unclear	yes[9]	unclear

Risk of bias (study level): EQUULEUS trial

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
no	no	no, open-label	no	yes[10]	high

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, D-Kd=daratumumab plus carfilzomib and dexamethasone, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, IMiD=immunomodulatory drug, Int.=intention, IRR=infusion-related reactions, ITT=intention-to-treat, Kd=Carfilzomib+dexamethasone, KdD=Carfilzomib+dexamethasone+daratumumab, MM=multiple myeloma, MRD=minimal residual disease, n=number of patients,

[6] 7 (8%) events were considered reasonably related to daratumumab, 15 (18%) events were considered reasonably related to carfilzomib, and 12 (14%) events were considered reasonably related to dexamethasone.
[7] death due to TEAE(s); 2 due to general physical health deterioration (not related to treatment) and 1 due to multiple organ dysfunction (possibly related to treatment).
[8] discontinuation due to TEAE(s); including grade 4 thrombocytopenia, grade 3 asthenia, grade 3 prostate cancer, and grade 2 back pain (1 case each).
[9] Industry-funded
[10] The study design and analyses were devised by the investigators and sponsor. The sponsor conducted the final data analysis and verified the accuracy of the data. Writing assistance was funded by the sponsor. The trial is ongoing until 07/2022.

NICE=National Institute for Health and Care Excellence, OR=Odds ratio, ORCA=Onyx Response Computer Algorithm, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PI=proteasome inhibitor, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent AEs

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