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COVID-19 and myeloma clinical research – experience from the CARDAMON clinical trial

COVID-19 – caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – has spread to over 213 countries and territories, with 24,021,218 cases, including 821,462 deaths, reported to WHO by 28 August 2020.¹ In the UK alone, there were 328,846 laboratory-confirmed cases and 41,465 COVID-19-associated deaths.² Self-isolation and physical distancing measures were implemented in most jurisdictions to limit the spread of the virus. Changes to clinical practice saw the short-term reduction of routine and non-emergency care to liberate much-needed capacity in medical facilities, while minimising the risk to patients and healthcare workers by eliminating avoidable face-to-face interactions.

Haematology patients were shown to be particularly vulnerable to SARS-CoV-2 infection³ and in need of shielding;

hence alternative management plans and new ways of delivering care were implemented wherever possible to reduce individual patient susceptibility.⁴ Various clinical guidelines were issued at unprecedented speed, including recommendations for multiple myeloma (MM) and patients needing stem cell transplantation (SCT).^{5–8} Conducting clinical trials in this environment poses unique challenges, having to strike a balance between patient safety, maintaining trial integrity, and ensuring adherence to good clinical practice (GCP) standards. The EMA, the EU Commission and the UK MHRA all published guidance to help stakeholders better manage clinical trials during the COVID-19 pandemic.^{9–11}

We report the challenges and adaptations made to the CARDAMON trial during the peak of the COVID-19

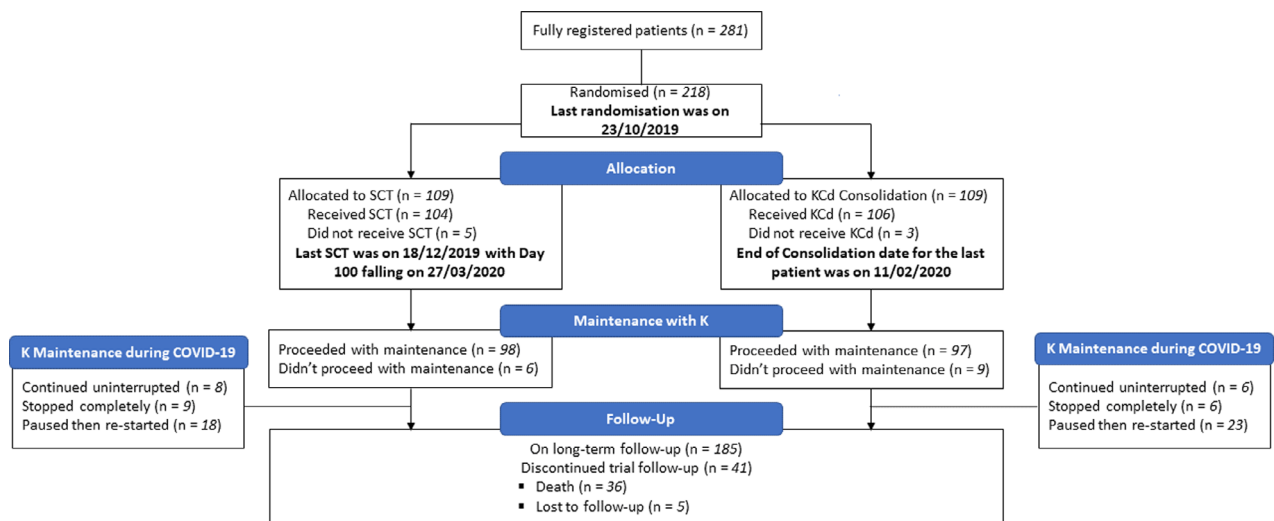


Fig 1. This flow diagram illustrates the progress through the various phases of the CARDAMON phase II clinical trial, including the impact of COVID-19 on the 70 patients on maintenance K across the two treatment arms at the start of the lockdown period. The 15 patients who stopped K maintenance joined the 170 patients who were already on long-term follow-up on 24 March 2020, bringing the number up to a total of 185. SCT, stem cell transplantation; K, carfilzomib; C, cyclophosphamide; d, dexamethasone.

outbreak in the UK in March–June 2020. CARDAMON is a phase II, randomised, open label clinical trial in transplant-eligible newly diagnosed MM (NDMM) that assesses the benefit of upfront SCT (clinicaltrials.gov identifier NCT02315716). Patients are treated with intravenous carfilzomib, cyclophosphamide and dexamethasone (KCd) as induction, then randomised to standard consolidation with SCT or to a further four cycles of KCd, following which all receive 18 months of maintenance with weekly single agent carfilzomib (d1, 8 and 15).¹² Aside from standard serological response assessments, minimal residual disease (MRD) was assessed by bone marrow (BM) sampling at prespecified timepoints, and by PET-CT for those patients on an imaging sub-study.

When the UK went into lockdown on 24 March 2020, 70 patients were still receiving carfilzomib maintenance and 170 were on follow-up (Fig 1). Adaptations to the trial protocol were agreed within the Trial Management Group (TMG), allowing CARDAMON to continue with minimal disruption. Local Principal Investigators (PIs) were informed of these changes, with open communication by email or telephone facilitating rapid resolution of further queries and efficient trial management throughout.

Assessments conducted locally or remotely

Pre-treatment blood tests could be completed locally, either via the GP or at local hospitals, to save patient travel and footfall in the trial site, with results sent to the site for review before carfilzomib dosing. Monthly follow-up visits were permissible via telephone or video conferencing, initiating in-person assessment and/or investigations as clinically indicated.

Pragmatic approach to treatment delays during carfilzomib maintenance

Patients who had completed at least 12 months of maintenance could stop treatment at the PI's discretion and the patient's wishes. Patients who completed <12 months of maintenance were encouraged to continue if possible, allowing delays of up to 14 weeks, compared to four weeks in the pre-COVID-19 era. For those who had completed maintenance therapy, end of maintenance assessments could be completed outside of the 14-day time-window.

Restarting carfilzomib maintenance with step-up dosing after treatment break

Initiation of carfilzomib therapy is routinely done with a step-up dose from 20 mg/m² to target dose (56 mg/m² in CARDAMON). To reduce the risk of infusion reactions and adverse events, such as thrombotic microangiopathy occurring on resuming therapy after a break,¹³ an urgent safety measure was implemented. Where carfilzomib maintenance was delayed for >4 weeks, treatment was to be restarted at

20 mg/m² on day 1 of the new cycle before escalating to the full 56 mg/m² or last tolerated dose.

Postponement of six-month MRD assessment during maintenance

BM sampling for MRD assessments, due at six months of maintenance, could be delayed for up to three months, and similarly for the follow-up PET-CT scan, also due at six months.

Impact on CARDAMON trial activity

During lockdown, 15 patients stopped carfilzomib maintenance completely after a median of 15 cycles (range 5–18), six of whom completed < 12 (median seven cycles; range 5–8); 14 carried on uninterrupted and 41 patients restarted after a median treatment pause of 12 weeks (range 8–19.6). These protocol amendments allowed 55 patients who would otherwise have stopped trial treatment to stay on carfilzomib maintenance on the CARDAMON study (Fig 1). Of 25 outstanding MRD BM assessments, 20 were delayed by a median of two months (range 1–3), with investigations resuming when restrictions eased in June. As of 5 August 2020, eight of the delayed BM assessments have been performed, while three patients declined. PET-CT scans were delayed in 6/9 patients, of which two have been performed.

Effect on data analysis and interpretation

Although all patients completed the randomised component of trial treatment by 29 February 2020, delays and alterations to maintenance therapy may not have affected the two arms equally. PIs may be potentially biased to alter treatment based on local COVID-19 clusters and patients' favourable MM response. Therefore, sensitivity analyses will be performed with and without the inclusion of affected patients to assess the significance of the measures taken on patient outcomes. Secondary outcomes will also be assessed as originally intended in both pre- and post-COVID-19 scenarios.

This global crisis should encourage the rethinking of study designs to make future clinical trials more flexible and pragmatic. Prompt and practical action successfully mitigated the unavoidable disruption of CARDAMON, protecting patient safety while maintaining trial conduct and optimising scientific integrity. Successful adaptations worth retaining beyond the pandemic include flexibility around remote clinic visits and investigation timing to help improve protocol adherence and trial dropout rates. The postpandemic environment comes with risks of missing or delayed data collection in ongoing trials, possibly impacting data analysis and interpretation. More patient-centric study designs that maximise translatability to routine practice may improve research efficiency and outcomes while enhancing patient safety and experience.¹⁴

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