Optimising therapeutic outcomes of patients with haematological malignancies (multiple myeloma)

Faouzi DJEBBARI

This thesis is submitted in partial fulfilment of the requirements of Kingston University for the degree of:

"Doctor of Philosophy by publication"

School of Life Sciences, Pharmacy and Chemistry

Kingston University

Supervisors:

Dr Shereen El Nabhani

Professor Helmout Modjtahedi

September 2020

DECLARATION

The management of haematological malignancies witnessed a major revolution in the last 10 years, which significantly improved survival outcomes, owing to the advent and approval of a number of life-saving systemic anticancer therapies (SACT). However, there remain a number of unmet needs, which can be addressed by understanding how to optimise the use of available therapies in order to improve outcomes of patients with haematological cancers.

I am an Advanced Haematology Pharmacist working at Oxford University Hospitals NHS Foundation Trust. I have been practising in Oxford's myeloma clinic as an independent prescriber since 2015. I am passionate about improving clinical outcomes for patients with multiple myeloma. In the last 5 years, I have conducted a number of research projects and answered a number of research questions, which improved our understanding of how best to use certain novel agents to improve outcomes. In addition, a large part of my work focused on ameliorating current management strategies or introducing new measures to improve treatment efficacy whilst limiting toxicities and improving patients' quality of life (QoL).

I developed an extensive portfolio of research, by designing, leading, and completing a number of research projects, originating from the unmet need in clinical practice. My work resulted in numerous research papers published in prestigious peer-reviewed journals, and which are eligible for inclusion in my thesis.

Key multiple myeloma studies which I have conducted, have been carefully picked for inclusion, in a manner where they coherently fit together to redact a PhD by publication thesis "introductory section".

I declare that no material contained in this thesis has been used in any other submission for an academic award.

I declare that all material in this thesis is my original work and that any references to or use of other sources has been clearly acknowledged within the text.

Faouzi Djebbari

ACKNOWLDGEMENTS

I would like to thank my family for their support and encouragements and for their belief in my abilities to pursue a career in clinical research, and to overcome any challenges that come my way.

This extensive body of work was only made possible thanks to the full support of Dr Karthik Ramasamy (Lead Myeloma Clinician for Thames Valley Cancer Network, UK). He completely believes in the difference that haematology pharmacists can make to optimise therapeutic outcomes of myeloma patients. He acted as my senior author for all myeloma research studies, which I conducted in the last 5 years. He helped me to develop my research skills, and provided me with invaluable feedback to improve the quality of my work. He also supported me in disseminating my research findings across the various national, European and international haematology conferences.

I would also like to thank Professor Nicola Stoner (Consultant Cancer Pharmacist and my line manager). She is forward-thinking and has supported me fully in practicing research, which remains to date a relatively new platform for pharmacists.

Dr Toby Eyre (Lymphoma Consultant) has also contributed to the development of my research career, by offering opportunities for collaborative research, developing my research skills and methods, and mentoring me whilst conducting lymphoma research projects.

Last but not least, I would like to thank Dr Shereen El Nabhani (my PhD supervisor). She has mentored me very closely throughout my time as a Kingston University PhD Student, and supported me enormously during the write up of this thesis. Shereen is one of the most positive and supportive academics I have come across. I would like to equally thank Prof Helmout Modjtahedi, my second supervisor for his advice and invaluable support.

AUTHOR STATEMENT CONCERNING AUTHORSHIP

This extensive body of work includes a total of 20 papers: 16 research papers covering both multiple myeloma and lymphoma, and 4 review articles (non-research). For research papers, I was the first author of 10 papers, joint first author of 1 paper, and a co-author in 5 papers. I am also the first author of all 4 review articles.

To produce a coherent PhD thesis, I have decided along with my supervisors to focus on 8 myeloma-related research papers, which I have numbered below as key publications (KP): 1-8). I was the first author of 7 papers and a joint first author of 1 paper.

As a result of the good clinical research skills and output I demonstrated in myeloma, I also extended my research skills and knowledge by contributing to novel work relating the therapeutic management of lymphoma. I was the lead author or a key collaborator in a number of lymphoma research projects, which answered urgent clinical questions, relevant to clinical practice. I elected not to discuss lymphoma projects in this PhD introductory section, because I wanted the thesis to be very coherent, with a special focus on multiple myeloma. But, I have briefly described my main lymphoma studies at the end of the thesis under Appendix 1 titled "other publications not included in this thesis".

As required, hereby I provide a percentage estimate of my contribution to each of the 8 KPs describing the key myeloma studies included in this thesis. A Brief summary of this information can also be cross-checked on the "author contribution section" of each of the individual papers and also in Appendix 3 of this thesis, which contains the letters provided by senior authors to confirm those contributions.

- **KP1: Djebbari F**, Srinivasan A, Vallance G, Moore S, Kothari J, Ramasamy K (2018) Clinical outcomes of bortezomib-based therapy in myeloma. PLoS ONE. 2018: 13(12)

  Used under the open access license "CC-BY" (https://journals.plos.org/plosone/s/licenses-and-copyright). No further permissions are required for re-use of figures

  This study was originally led by my joint-first author. I participated initially in this study by taking part in the fortnightly myeloma research meetings, and contributed to data collection. I contributed to the interpretation of results. Later on, I led on the prioritisation of findings, writing and publishing the manuscript, and responding to peer-reviewers. I estimate my total contribution at 30-40%

- **KP2: Djebbari F**, Hubenov H, Neelakantan P, Wolf J, Offer M, Khera A, Louka E, Vallance G, Kothari J, Moore S, Ramasamy K. Carfilzomib therapy for relapsed myeloma: results of a UK multicentre experience. Br J Haematol. 2020; 188(4):57-60

  Statement from Wiley Online Library (Publisher for BJHaem): "AUTHORS - If you wish to reuse your own article (or an amended version of it) in a new publication of which you are the

author, editor or co-editor, prior permission is not required (with the usual acknowledgements)."

I designed the study, and its methodology. I collected the majority of the data and co-ordinated the progress of this project across the different UK participating centres. I analysed all the data. I led on writing and publishing the manuscript. I estimate my contribution at 75%

- **KP3: Djebbari F**, De Abrew K, Salhan B, Panitsas F, Hossain ME, Eyre TA, Willan J, Ramasamy K, Basu S, Jenner M, Kothari J. DPACE-based chemotherapy in the era of myeloma novel agents: a UK multicentre study. Eur J Haematol. 2020. DOI:10.1111/ejh.13422

  Statement from Wiley Online Library (Publisher for EJH): "AUTHORS - If you wish to reuse your own article (or an amended version of it) in a new publication of which you are the author, editor or co-editor, prior permission is not required (with the usual acknowledgements". Permission received from John Wiley and Sons and Copyright Clearance Center to re-use Figure 1:
  (https://s100.copyright.com/CustomerAdmin/PLF.jsp?ref=332737d9-d832-453f-93c4-6dca1b1d348d)

  I designed the study and its methodology. I collected Thames Valley data. I conducted data analysis and interpretation. I presented initial findings at the European Haematology Association Conference 2019 and International Myeloma Workshop 2019. I led on writing and publishing the manuscript. My total contribution is estimated at 70%.

- **KP4:** Sharpley FA, **Djebbari F**, Fourali S, Kothari J, Lynes JA, McLain-Smith S, Ramasamy K. Clinical outcomes with fixed-duration therapy (UK real-world data) compared with continuous lenalidomide and low-dose dexamethasone therapy (FIRST trial; MM-020) for transplant-ineligible patients with newly-diagnosed multiple myeloma. Leuk Lymphoma. 2020;61(3):732-736
  Used for this introductory section under the Creative Commons CC-BY-NC-ND license (https://creativecommons.org/licenses/). Figures 1 and 1S were used following permission obtained from Taylor and Francis Online (https://www.tandfonline.com/).

  I was a joint first author as documented on the published paper. I contributed significantly towards the conceptualisation, study design, methodology, data collection and analysis. My other joint first author moved jobs in the middle of this project, so I led on all aspects thereafter. I worked closely with the pharmaceutical company "Celgene" and medical statistics company "PH associates" to analyse data and meet study objectives. I contributed significantly towards writing the manuscript and publication. I estimate my contribution at least 50%

- **KP5: Djebbari F**, Sharpley FA, McLain-Smith S, Vallance G, Eyre TA, Kothari J, Moore S, Ramasamy R. Treatment-free interval as an additional measure of efficacy in a large UK dataset of transplant ineligible myeloma patients. PLoS ONE. 2020 15(2)

Used under the open access license "CC-BY" (https://journals.plos.org/plosone/s/licenses-and-copyright). No further permissions are required for re-use of figures

I designed the study and its methodology, along with my supervisor. I collected data and contributed towards the analysis. I led the management part of this study, and worked closely with the medical statistics company "PH associates" to complete statistical analysis and meet study objectives. I led on writing and publishing the manuscript. I estimate my total contribution at 75%.

- **KP6: Djebbari F**, Stoner N, Lavender V. Non-conventional dosing of oral anticancer agents in oncology and malignant haematology: a systematic review protocol. Sys Rvs Journal. 2017; 6(1):244.

  Used for this introductory section under the Creative Commons Attribution license "CC-BY" (https://www.biomedcentral.com/about/policies/reprints-and-permissions)

  I contributed towards the conception and design of this systematic review protocol. I led on all aspects of this project. I conducted testing and refinement of the literature search strategy and made a major contribution to writing the manuscript. I estimate my total contribution at 75%.

- **KP7: Djebbari F**, Stoner N, Lavender V. A systematic review of non-standard dosing of oral anticancer therapies. BMC Cancer. 2018; 18(1):1154.

  Used for this introductory section under the Creative Commons Attribution license "CC-BY" (https://www.biomedcentral.com/about/policies/reprints-and-permissions). No further permissions are required for re-use of figure 1

  I contributed towards the conception and design of this systematic review. I conducted the full search strategy and obtained the results. I contributed towards the inclusion/exclusion of studies, and quality appraisal. I extracted all data from included studies, and synthesised data. I led on manuscript writing and publication. I estimated my total contribution at 75%.

- **KP8: Djebbari F**, Panitsas F, Eyre TA, Prodger C, Davies F, Burton K, Khera A, Vallance G, Moore S, Kothari J, Peniket A, Ramasamy K. Infection-related morbidity in a large study of transplant non-eligible newly diagnosed myeloma patients treated with UK standard of care. Haematologica. Epub 2020 Jan 09. PMID: 31919073

  Accessed from Haematologica Journal website http://www.haematologica.org. Permission to re-use Figure 1 was obtained from Ferrata Storti Foundation.

  I designed the study and its methodology and contributed to data collection. I led on the management of this study and contributed significantly to data analysis. I led on writing and publishing the manuscript. I estimate my total contribution at 75%.

ABSTRACT

Multiple myeloma (MM) is a haematological malignancy of plasma cells. It is caused by an uncontrolled proliferative behaviour of clonal B cells. Cancer Research UK reported around 5820 new cases each year (2% of all cases) making it the 19th most common cancer. MM remains an incurable disease with a relapsing and a remitting course. The 5-year and 10-year survival rates in England are reported to be 52.3% and 29.1% respectively.

However, clinical outcomes have improved significantly in the last decade because of the increased availability of novel agents (oral and parenteral) in UK clinical practice, prescribed using one of two main strategies: fixed duration therapy (FDT) or continuous therapy (CT). These agents demonstrated their safety and efficacy in large phase 3 randomised clinical trials.

Real-world data remains equally as important as clinical trials because it allows the myeloma community to understand the global variations in clinical practice, and reported outcomes of these therapies in the real-world. Advanced age, frailty and co-morbidities often exclude real-world patients from clinical trials. This created a gap in the literature about efficacy of novel therapies for those patients. A better understanding of outcomes in the real-world is, therefore, required.

This introductory section presents my contribution to myeloma real-world research and to the optimisation of therapeutic outcomes of novel therapies used to treat this condition, through 6 different retrospective real-world studies and one large systematic review.

KP1 of 272 bortezomib patients demonstrated that cumulative dose ≥50mg is associated with improved efficacy outcomes. KP2 of 30 carfilzomib patients demonstrated that this therapy is efficacious and has a reasonably good tolerability profile (comparable to ENDEAVOR trial). The study also demonstrated how dose attenuation should be considered early on in elderly patients or those with cardiac morbidities, to improve tolerability.

KP3 of 59 DTPACE patients demonstrated that this intensive cytotoxic chemotherapy can be beneficial in extending time to next treatment (TTNT) if consolidated with an autologous stem cell transplant (ASCT). Conversely, it appears to be of less benefit in non-ASCT-eligible patients, or those more heavily pre-treated.

In KP4 which compared FDT (n=223) in the real-world to CT (n=253), FDT conferred inferior overall survival (OS), progression-free survival (PFS), and TTNT compared to CT. KP5 of 292 patients demonstrated that the median treatment-free interval (TFI) after 1st line therapy was 6.9 months and declined with subsequent treatment phases. The same trend was observed in the different age and co-morbidity subgroups.

The large systematic review of evidence of non-standard dosing of 78 different oral anticancer agents (KP6 and KP7) identified 34 papers eligible for inclusion, of which two were myeloma studies and showed limited evidence: one for thalidomide and one for lenalidomide.

In KP8 which investigated infection-morbidity in 200 elderly myeloma patients, a number of baseline clinical predictors of infective episodes were identified, such as raised baseline lactate dehydrogenase (LDH) levels, chronic obstructive pulmonary disease (COPD) and smoking history.

In summary, this introductory section will describe the real-world outcomes of myeloma patients treated with a number of novel agents and using different modalities. This thesis will discuss strategies/recommendations to optimise outcomes of those therapies, and to improve tolerability.

LIST OF FIGURES

(https://www.biomedcentral.com/about/policies/reprints-and-permissions). The publisher of this article confirmed that no further permissions are required. .

Figure (7): Cumulative incidence curses of infections: A) Cumulative incidence curves of all infections according to elevated LDH, B) Cumulative incidence curves of ≥G3 infections according to elevated LDH, C) Cumulative incidence curves of all infections according to COPD, D) Cumulative incidence curves of ≥G3 infections according to COPD, E) Cumulative incidence curves of all infections according to smoking, F) Cumulative incidence curves of ≥G3 infections according to smoking (KP8). This figure is obtained from Figure 1 of (Djebbari et al 2020, Haematologica), accessed from Haematologica Journal website (http://www.haematologica.org). Permission to re-use Figure 1 was obtained from Ferrata Storti Foundation.

LIST OF ABBREVIATIONS

AE: Adverse events

AUC: Area under the curve

BNF: British National Formulary

CA: chromosomal abnormalities

CarDex: carfilzomib with dexamethasone

CCI: Charlson Co-morbidity Index

CI: confidence intervals

COPD: chronic obstructive pulmonary disease

CR: complete response

CTCAE: Common Terminology Criteria for Adverse Events

CTDa: attenuated CTD

CF: cardiac failure

CNS: central nervous system

CRUK: Cancer Research UK

CT: computed tomography

CTD: cyclophosphamide, thalidomide, and dexamethasone

CINAHL©: Cumulative Index to Nursing and Allied Health Literature

DCEP: Dexamethasone, cyclophosphamide, etoposide and cisplatin

CVAE: cardiovascular adverse events

DLBCL: diffuse large B-cell lymphoma

D-VMP: daratumumab with bortezomib, thalidomide and dexamethasone

EHR: electronic health records

EMN: European Myeloma Network

FDT: fixed-duration therapy

FISH: fluorescent in situ hybridization

FIRST: Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide

G: grade

HR: hazard ratio

HRQoL: Health-related quality of life

ICU: intensive care unit

IsaPomDex: isatuximab with pomalidomide and dexamethasone

IDI: intended dose intensity

Igs: immunoglobulin

IMF: International Myeloma Foundation

IMiDs: immunomodulatory drugs

IMWG: International Myeloma Working Group

IQR: interquartile range

ISS: international staging system

IT: intrathecal

IV: intravenous

LDH: lactate dehydrogenase

MP: melphalan with prednisolone

MPT: melphalan, prednisone, and thalidomide

MR: minor response

MRI: magnetic resonance imaging

MM: multiple myeloma

NDMM: newly diagnosed multiple myeloma

MVA: multivariate

NICE: National Institute for Health and Care Excellence

ORR: overall response rate

OS: overall survival

PI: proteasome inhibitor

PN: peripheral neuropathy

PR: partial response

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

PS: performance status

R-CHOP: rituximab with doxorubicin, cyclophosphamide, vincristine and prednisolone

Rd: lenalidomide with dexamethasone

RDI: relative dose intensity

RMM: relapsed multiple myeloma

R-GCVP: rituximab with gemcitabine, cyclophosphamide, vincristine and prednisolone

SACT: Systemic anticancer treatments

SC: subcutaneous

sCR: stringent complete response

sFLCs: serum free light chains

SPC: Summary of Products Characteristics

TE: transplant eligible

TNE: transplant non-eligible

TTNT: time to next treatment

TVCN: Thames Valley Cancer Network

TFI: treatment-free interval

UV: univariate analysis

VD: bortezomib with dexamethasone

VGPR: very good partial response

VMP: bortezomib, melphalan, and prednisone

VTD: bortezomib with thalidomide and dexamethasone

WCRFI: World Cancer Research Fund International

CONTENTS

1. INTRODUCTION TO MULTIPLE MYELOMA:

Multiple myeloma (MM) is a haematological malignancy of plasma cells (Bianchi et al 2014; Ramasamy et al 2015). It is caused by an uncontrolled proliferative behaviour of clonal B cells (Bianchi et al 2014; Ramasamy et al 2015). These cells secrete a dysfunctional monoclonal immunoglobulin or a fragment called paraprotein (Kyle et al 2009; Bianchi et al 2014; Ramasamy et al 2015). Normal immunoglobulins are affected as a result, which predisposes patients to increased risk of infections (Bianchi et al 2014). In addition, the clonal cells displace the normal bone marrow causing a complex series of clinical symptoms such as anaemia, fatigue, bone resorption causing lytic lesions and/or fractures, hypercalcaemia, renal dysfunction, and neurological symptoms (Palumbo et al 2011; Bianchi et al 2014; Ramasamy et al 2015). MM can also be non-secretory in some cases (Bianchi et al 2014; Ramasamy et al 2015).

1.1. Epidemiology and risk factors:

MM accounts for about 0.8% of all cancer types worldwide with 114000 new cases reported in 2012 (Ramasamy et al 2015; WCRFI 2016). In the UK, Cancer Research UK (CRUK) statistics reported annually around 5820 new diagnoses, which counts for 2% of all new cases, making it the 19th most common cancer (CRUK 2017). The number of myeloma reported deaths each year stands at 3000 (CRUK 2017). In 2013-2017, the 5-year and 10-year survival rates in England were 52.3% and 29.1% respectively (CRUK 2017).

The precise aetiology of myeloma is unknown and the inherited risk remains to be fully understood, but a number of risk factors have been established (Ramasamy et al 2015). This includes old age, male sex, African or African-American ethnicity, genetics, and history of monoclonal gammopathy of undetermined significance (Ramasamy et al 2015; CRUK 2016).

1.2. Diagnosis:

Early diagnosis of myeloma is required in order to improve survival and clinical outcomes (Ramasamy et al 2015). A number of diagnostic tests are initially required during the first presentation with suspected myeloma (Dimopoulos et al 2011; Ramasamy et al 2015). These include a full blood count, bone, liver, and renal biochemistry profiles (albumin, calcium, creatinine and lactate dehydrogenase (LDH)), serum β^2 microglobulin, serum immunoglobulins (Igs), serum electrophoresis and immunofixation, and serum free light

chains (sFLCs) (Dimopoulos et al 2011; Ramasamy et al 2015). In addition, patients undergo a bone marrow aspiration and biopsy (Ramasamy et al 2015). Imaging is also used to screen and diagnose patients with skeletal surveys, CT and MRI scanning (Ramasamy et al 2015).

1.3. Myeloma staging and risk stratification:

Risk stratification of myeloma patients defines specific pathways of management, and helps to rationalise drug therapies (Chng et al 2014).

The international staging system (ISS) for myeloma is a prognostic tool for myeloma patients. It combines serum β2 microglobulin and serum albumin to stage myeloma as I (Serum β2 microglobulin <3.5 mg/L and serum albumin ≥ 3.5 g/dL) where median overall survival (OS) is 62 months, II (serum β2 microglobulin <3.5 mg/L but serum albumin <3.5 g/dL, or serum β2 microglobulin 3.5 – 5.5 mg/L irrespective of serum albumin) where median OS is 44 months, and III (serum β2 microglobulin >5.5 mg/L) where median OS is 29 months (Ramasamy et al 2015).

The detection of chromosomal abnormalities (CA) by fluorescent in situ hybridization (FISH) is an important factor which defines the biological features of myeloma at presentation. For instance, in the newly diagnosed myeloma (NDMM) setting, high-risk disease presents with del (17p) and/or translocation t (4; 14), and/or translocation t (14; 16) and is associated with a median overall survival (OS) of 24.5 months (Palumbo et al 2015). However, standard-risk disease does not present with any of the chromosomal abnormalities previously mentioned, and is associated with a significantly higher OS of 50.5 months ($P < 0.001$) (Palumbo et al 2015).

Serum LDH is another key element in defining myeloma characteristics. Elevated LDH is an indicator of aggressive disease and/or a high proliferation rate, or extramedullary presentation, and is a predictor of poor prognosis (Dimopoulos et al 1991).

Taking into account all of ISS, cytogenetics and serum LDH, the International Myeloma Working Group (IMWG) published a report which assessed pooled data from 4445 patients enrolled in 11 international clinical trials, based on which a simple and reliable tool named "revised ISS" or "R-ISS" was designed to help stratify myeloma patients at presentation with regard to the relative risk to their survival (Palumbo et al 2015). There are 3 categories in R-ISS: category I (described as ISS stage I and standard-risk cytogenetics and normal LDH), category II (described as not I or III), and category III (described as ISS stage III and either

high-risk cytogenetics or high LDH) (Palumbo et al 2015). R-ISS has shown to be a simple and powerful prognostic staging system and is currently adopted in UK myeloma clinical practice.

1.4. Therapeutic management of myeloma:

MM remains an incurable disease with a relapsing and a remitting course. Newly diagnosed patients are treated with first line therapy to achieve a deep and durable response, but eventually relapse and start 2nd and subsequent lines of therapy.

Historically, MM is sensitive to many cytotoxic chemotherapy drugs such as alkylating agents (cyclophosphamide, melphalan), anthracyclines (e.g. doxorubicin), vinca-alkaloids (e.g. vincristine), and to corticosteroids (e.g. dexamethasone, prednisolone) (Kyle et al 2008). Treatment options have changed dramatically over the last two decades because of better disease understanding and major breakthroughs in therapeutics which revolutionised this field of haematology (Ramasamy et al 2015).

New efficacious treatments from various pharmacological classes offer clinicians the ability to tailor treatments to individual patients, taking into consideration co-morbidities and the toxicity profile of individual drugs (Bianchi et al 2014). These include doublet to quadruplet combinations with different agents such as oral immunomodulatory drugs (IMiDs): thalidomide, lenalidomide and pomaliomide; proteasome inhibitors (PIs): subcutaneous bortezomib, intravenous carfilzomib and oral ixazomib, monoclonal antibodies (daratumumab, isatuximab) and histone deacetylase inhibitors (panobinostat).

Starting treatment for NDMM is based on the assessment of clinical symptoms; particularly those suggestive of end organ damage (Ramasamy et al 2015). IMWG-recommended assessment also includes histology and monoclonal protein quantification, as well as radiological identification of focal bone lesions (Ramasamy et al 2015).

According to IMWG, active myeloma is defined as clonal bone marrow plasma cells >10% or biopsy-proven bony or extramedullary plasmacytoma plus one or more of the following four **CRAB** features which are regarded as evidence of myeloma-related end-organ damage: hyper**c**alcemia: serum calcium >0.25 mmol/L (>1mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11mg/dL), **r**enal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177mol/L (>2mg/dL), **a**naemia: haemoglobin value of >20g/L

below the lowest limit of normal, or a haemoglobin value <100g/L, and **b**one lesions: one or more osteolytic lesion on skeletal radiography, CT, or PET/CT (IMF, 2014).

A diagnosis of active myeloma can also be made if any one or more of the following biomarkers of malignancy are present, referred to as the **SLiM** criteria: **S**: ≥ **S**ixty-percent (≥60%) clonal BM plasma cells; **Li**=serum free **Li**ght chain ratio involved: uninvolved ≥100; **M**: ≥1 focal lesion (≥5 mm each) detected by **M**RI studies (IMF, 2014).

The decision on the most appropriate treatment for NDMM is governed by a variety of factors which include patient age, pre-existing co-morbidities, performance status (PS), ISS staging, cytogenetic risk, and transplant eligibility (Ramasamy et al 2015; WCRFI 2016).

Standard of care splits patients into two sub-categories. Transplant-eligible (TE) patients are those younger (typically ≤65 years) fit patients and will receive an induction regimen, which is then consolidated with high dose chemotherapy and an autologous stem cell transplant (ASCT) (Ramasamy et al 2015). For those who are transplant non-eligible (TNE), management takes into account old age, PS, co-morbidities, and frailty; and consists of an appropriate treatment regimen, which can achieve the best response and maintains disease control (Ramasamy et al 2015). Across all pre-specified subgroups of NDMM patients, the use of maintenance lenalidomide (as demonstrated in Myeloma XI trial) was shown to significantly improve progression-free survival (PFS) (Jackson et al 2019). Upon future relapses, both TE and TNE patients are treated with a subsequent line of therapy.

2. IMPORTANCE OF REAL-WORLD DATA IN MYELOMA:

Historically, patients diagnosed with active myeloma had a median OS of only around 3 years, with limited treatment options available (Anderson et al 2016). In the past 15 years, we witnessed an increasing range of highly active treatment options being investigated in randomised clinical trials, offering novel doublet to quadruplet combinations and demonstrating significant improvements in myeloma disease responses and patients' survival outcomes (D'Agostino et al 2019). As a result, the myeloma treatment landscape benefited from the incorporation of number of these novel agents/treatment regimen, which have become available in clinical practice as a result of safety and efficacy data demonstrated in a number of published large phase 3 randomised clinical trials.

Real-world data, however, remains equally as important because it allows the myeloma community to understand the global variations in clinical practice, and to evaluate the outcomes of these therapies in the real-world. Clinical outcomes in routine care were previously reported to be inferior to what has been reported in the clinical trial setting (Chari et al 2017; Richardson et al 2018). The CONNECT-MM registry is a prospective observational registry of patients with NDMM in the US. From this registry, trial-ineligible patients demonstrated a significantly lower 3-year OS rate compared to their trial-eligible counterparts (63% vs 70%; $p < 0.05$) (Shah et al 2017). A prospective clinical cohort study from the German registry "Tumour Registry Lymphatic Neoplasms (TLN)" recruited 285 non-transplant patients with NDMM at the start of frontline therapy and categorised 30% of those patients as trial-ineligible (Knauf et al 2018). Median PFS and OS in the trial-ineligible subgroup were inferior compared to the trial-eligible subgroup (Knauf et al 2018).

The differences between clinical trials and the real-world in myeloma:

The gap between therapy effectiveness in the real-world compared to safety and efficacy reported in clinical trial data lies in the characteristics that distinguish the two settings. The primary factor leading to this gap is the strict eligibility criteria to enrol patients in clinical trials; as demonstrated by the CONNECT-MM registry which reported that 40% of its patients were trial-ineligible (Shah et al 2017). This data was obtained by looking at common

exclusion criteria collected from 16 published myeloma clinical trials, then categorising patients in this registry according to their potential for trial eligibility. The stringent selection criteria in clinical trials exclude a significant proportion of the real-world population.

A US electronic health records (EHR) of 1265 real-world patients was retrospectively evaluated to identify representativeness of these patients (trial-eligible or ineligible) using eligibility criteria of 6 different hallmark randomised controlled trials (ASPIRE, TOURMALINE-MM1, ELOQUENT-2, POLLUX, CASTOR and ENDEAVOR) (Chari et al 2020). The authors described a variation in the ineligibility rates for each individual trial, with up to 72.3% (range: 47.9%-72.3%) (Chari et al 2020). The authors also found that factors such as other malignancies, cardiovascular disease, acute infection, and renal impairment were the common reasons for trial ineligibility (Chari et al 2020). In addition, the study demonstrated that advanced age, Charlson comorbidity score of ≥2, later therapy lines (3-4), and refractoriness to the previous therapy were independently predictive of trial ineligibility (Chari et al 2020). In addition, the study reported that trial-ineligible patients had a significantly greater mortality risk (Chari et al 2020). Another study, from the Danish multiple myeloma registry, demonstrated that the majority of NDMM patients do not fulfil the inclusion criteria in phase 3 clinical trials (Klausen et al 2019).

As a result, efficacy outcomes reported in the trial setting do not always translate into the real-world (Shah et al 2017). Patient-related factors which characterise real-world cohorts include advanced age, frailty, co-morbidities, organ dysfunction, poor performance status, advanced or aggressive/rapidly progressing disease. The latter are typical exclusion criteria from clinical trials, and this can drive the differences in safety and efficacy outcomes in routine care (Costa et al 2016; Shah et al 2017; Pulte et al 2018).

In additions, patients from community centres are often under-represented because clinical trials tend to be open for recruitment mainly in regional/academic cancer centres. Besides, physicians in the trial setting are required to follow protocol-driven dose modification, which may lead to better tolerability and longer duration of therapy, compared to routine care.

Patients in the real-world carry a higher toxicity burden from therapeutic interventions, particularly elderly patients or those with co-morbidities. Although we are observing a significant improvement in survival outcomes, a number of the novel and complex regimens currently in use can be associated with additional toxicity, which raises the new challenge of how to maintain patients on therapy, and how to achieve a high level of adherence. Besides, a

key difference between routine care and the clinical trial setting is that decisions about disease management strategies and therapy goals in clinical practice are mostly driven by patient's and physician's preference and motivation, as opposed to the strict adherence to the protocol, which is required in a clinical trial. For instance, the higher incidence of early treatment discontinuation in the real-world compared to clinical trials can be multifactorial, for reasons such as: patient mobility, distance from the treating institution, and the number of hospital visits involved in the delivery of myeloma therapy.

Another key factor which can drive a difference in outcomes between the two settings lies in the significant variations between healthcare systems and clinical practices that exist across the world, and sometimes within an individual country. Moreover, a number of studies suggested that the decision to delay the initiation of therapy until a symptomatic relapse occurs (which is the practice we commonly observe in routine care) compared to starting therapy at the point of biochemical relapse, may be associated with inferior outcomes (Katodritou et al 2018; Lopez et al 2015).

Understanding the difference in characteristics between the two settings helps to explain the difference in clinical outcomes for myeloma patients. But, equally as important is gaining an understanding of which elements are important from a patient's perspective and which factors drive their treatment decision and their myeloma journey, to help researchers gain a greater understanding of the difference observed in outcomes.

Understanding what is important for patients in the real-world:

Patients in the real-world prioritise the need for a rapid control of system during the symptomatic presentation of the disease, because MM is associated with the highest symptom burden across all haematological malignancies (Johnsen et al 2009). Another important consideration is patients' desire to achieve a good QoL by maintaining their activities of daily living. Impairment in QoL as a result of myeloma symptoms, treatment-related toxicities, or hospital inpatient admissions, can all adversely impact the treatment journey of patients and negatively affect their experience.

Patients highly value a treatment option which is convenient. For instance, some patients prefer oral treatments over parenteral drug administration even with the knowledge about the inferior efficacy outcomes sometimes expected from this choice (Wilke et al 2018), because

they suffer from co-morbidities, or they have reduced mobility which affects their ability to attend hospital visits, or they prefer oral treatments because those have a minimal impact on their ability to go to work.

Treatment-related toxicities can pose a significant burden to patients. Real-world datasets previously highlighted the impact of toxicities on the rate of treatment discontinuation in all myeloma settings (Jagannath et al 2016; Yong et al 2016). In addition, a reduced duration of therapy in the real-world because of toxicities can lead to inferior outcomes compared to phase 3 trial data.

Moreover, as the management of myeloma is increasingly moving towards an individualised strategy empowered by patient choices, optimal efficacy outcomes and goals of therapy can mean different things to different patients. For instance, one patient may choose the continuous therapeutic strategy with a novel agent/regimen to achieved a long PFS, whereas another patient who highly values the treatment-free remission period to restore their QoL, may decide to discontinue therapy after a number of treatment cycles once a deep response is achieved, which in turn can confer different long term clinical outcomes.

The importance of conducting real-world research described in this thesis:

In order to address the gap in clinical outcomes between clinical trials and routine care and to support patients in routine care to experience a positive treatment journey, more real-world data are required on MM disease characteristics, treatment patterns and outcomes from unselected patients with advanced age and/or co-morbidities. In view of the importance of conducting real-world research in myeloma therapeutics and the need to understand current outcomes in the UK and devise strategies to optimise them in the future, I have performed a number of clinical studies in the era of novel agents.

I elected to describe eight of those studies in my PhD thesis. Each of these studies are discussed separately and will focus on literature review, rationale for study, brief description of results, in addition to the contribution of my research to the literature and the resulting changes in clinical practice.

Three of the studies investigated outcomes of different therapeutic agents/regimen: bortezomib (KP1), carfilzomib (KP2) and DPACE (KP3). Two of the studies investigated

new treatment strategies: continuous vs. fixed-duration therapy (KP4) and treatment-free interval (KP5). Three of my research papers investigated how to improve tolerability of myeloma treatments in the real-world: systematic review protocol of non-standard dosing of oral treatments (KP6), the systematic review findings (KP7) and the infection-related morbidity study in elderly myeloma patients (KP8).

3. Optimising outcomes of myeloma therapies:

3.1. Improving outcomes of bortezomib usage:

3.1.1. Literature review and rationale of study:

Bortezomib, the first-in-class proteasome inhibitor, remains a widely used anti-myeloma agent, despite licensing of newer agents. Its use in combination with other agents, is standard of care and is approved by the UK's National Institute for Health and Care Excellence (NICE) to treat NDMM, in the TE setting (at 1.3mg/m^2 twice weekly for up to 24 doses) in combination with dexamethasone as per IFM trial; or with dexamethasone and thalidomide, as per PETHEMA trial) (NICE 2014). Bortezomib is also NICE-approved to treat NDMM in the TNE setting (for a total of 51 doses) in combination with an alkylating agent (melphalan) and a corticosteroid (prednisolone), as per VISTA trial (NICE 2011). In the relapsed (RMM) setting, it is approved (for a maximum of 32 doses) in combination with dexamethasone as per APEX trial (NICE 2007).

The influence of the route of bortezomib administration was investigated in a phase III multicentre study which randomised 222 RMM patients to either iv or sc bortezomib at 1.3mg/m^2 twice weekly for up to 8 cycles (Moreau et al 2011).The study showed that sc route offers non-inferior efficacy to iv (Moreau et al 2011). However, peripheral neuropathy (PN) was significantly less common in the sc arm compared to iv: any grade (G) was (38% vs. 53%, p=0.044), G2≥ (24% vs. 41%, p=0.012), and G3≥ (6% vs. 16%, p=0.026) (Moreau et al 2011).

The influence of the frequency of bortezomib administration (once weekly vs. twice weekly) was investigated in a post-hoc analysis of a phase III trial (Bringhen et al 2010). This study showed that long term efficacy was similar between once and twice weekly bortezomib, and incidence of G 3/4 PN was significantly lower with weekly frequency (8% vs. 28%, p< .001) (Bringhen et al 2010).

Based on the above data, clinical practice has adopted some changes in bortezomib usage to improve tolerability and optimise outcomes (e.g. dosing frequency from twice weekly to once weekly, choice of alkylating agent, and switching from iv to sc route to reduce PN).

Along with my colleagues, I set out to study clinical outcomes of bortezomib in clinical practice both in the NDMM and RMM settings in a large cohort of patients treated within the regional Thames Valley Cancer Network (TVCN) in the UK. The aim was to assess factors

influencing efficacy outcomes. This work was published in PLOS ONE and the paper will be referred to herein as key publication 1 (KP1).

3.1.2. Methodology:

The study described in KP1 included adult patients with a diagnosis of symptomatic MM, treated between 2010 and 2016 with a bortezomib-based regimen for NDMM (first line therapy) or for RMM (therapy for relapse) (KP1). The study was approved by the regional Oxford University Hospitals NHS Foundation Trust across all TVCN participating sites.

The chemotherapy prescribing database and the medical records of 272 patients were used to collect data on a number of patient, disease and treatment characteristics. Data on bortezomib adverse events (AEs) were not collected because the toxicity profile is well established from clinical studies. However, the proportion of patients discontinuing therapy due to AEs was recorded (KP1). Two main clinical outcomes were evaluated: OS and TTNT (KP1).

We investigated the influence of the following factors on OS and TTNT: sex, age (<75 vs. ≥ 75 years), ASCT, combination (doublet vs. triplet), cumulative bortezomib dose (<50mg vs. ≥50mg), and route of administration (sc vs. iv) (KP1). We also conducted univariate (UVA) and multivariate (MVA) analyses (KP1).

3.1.3. Key results:

KP1 results demonstrated that in the total cohort of 272 patients, route of administration (iv vs. sc) influenced neither OS ($p = 0.5$), Fig (1A), nor TTNT ($p = 0.052$). Dose intensity analysis demonstrated that median OS was statistically longer in patients receiving a cumulative bortezomib dose of ≥50mg compared to <50mg ($p = 0.003$).

In those who received <50mg (n=148), we performed further in-depth analysis and identified the following reasons for bortezomib discontinuation: treatment goal achieved (44%), intolerable toxicities (15%), disease progression (12%), death (16%), and unknown cause in the remainder (KP1).

In the NDMM cohort, there was a trend for improved OS and TTNT with triplets compared to doublets but this was not statistically significant, Fig (1C). Administration of a higher cumulative dose (≥50mg) resulted in a longer median OS but without reaching a statistical significance, Fig (1D) (KP1). In the RMM cohort, triplets (compared to doublets) Fig (1E),

and a higher cumulative dose (Fig 1F) resulted in better OS but without statistical significance (KP1). When MVA Cox Regression analysis was performed, the following were identified as significant factors associated with improved OS: dose ≥50mg (p = 0.002) and ASCT (p = 0.002) (KP1).

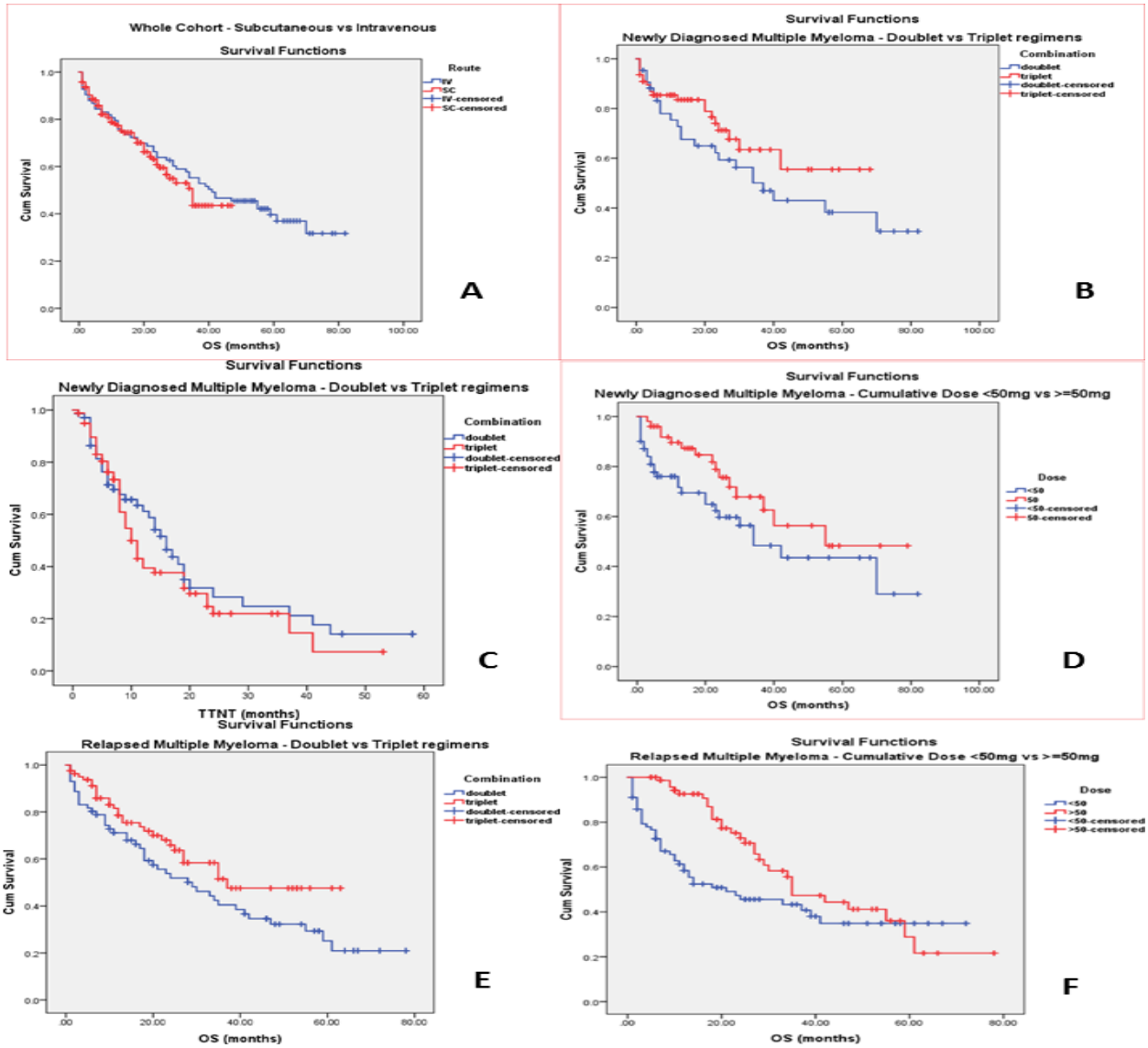


Figure (1): Outcomes of bortezomib therapies: A) OS in total cohort (sc vs. iv), B) OS in NDMM (doublet vs. triplet), C) TTNT in NDMM (doublet vs. triplet), D) OS in NDMM (≥50mg vs. <50mg), E) OS in RMM (doublet vs. triplet), F) OS in RMM (≥50mg vs. <50mg). (KP1). This figure is adapted from Figures 1-6 of (Djebbari et al 2018, PLOS ONE) under the open access license "CC-BY" (https://journals.plos.org/plosone/s/licenses-and-copyright). The publisher confirms that no further permissions are required.

3.1.4. Impact of my research and future directions:

This study examined bortezomib usage in clinical practice and helped provide information to myeloma clinicians, which can contribute to the optimisation of clinical outcomes. KP1 data reporting no difference in OS or TTNT according to route of administration (iv vs. sc) adds to the body of evidence (KP1). Evidence of similar bortezomib efficacy with either route has previously been published. Similar response rates of these routes, in both NDMM and RMM settings, were reported in a large Czech retrospective study of 446 patients (Minarik et al 2015). In addition, a large Italian study of 326 NDMM patients treated with VTD or VD, reported similar response rates (sc: 90% vs. iv: 80%, p=0.118) (Mangiacavalli et al 2017).

KP1 established that cumulative bortezomib dose ≥50mg is associated with improved OS and a delayed need to start a subsequent therapy (KP1). This is the first study to look at 50mg as a cut-off value for cumulative dose, and we have justified in the paper why we opted for this cut-off value. In clinical practice, patient could benefit from continuing bortezomib therapy to deliver a high cumulative dose (subject to tolerability) without early discontinuation, in order to deepen and/or extend myeloma response, and consequently improve outcomes. These findings add to the body of literature which suggested better OS according to cumulative dose. An analysis of 340 patient in VISTA trial who received bortezomib-based VMP therapy showed that median OS according to cumulative dose was (≥39mg/m^2: 66.3 vs. < 39mg/m^2: 46.2 months, $p < 0.0001$) (Mateos et al 2015).

KP1 also demonstrated that the impact of triplet vs. doublet on TTNT in either myeloma settings was modest, and the improvement in OS with triplets did not reach statistical significance (KP1). Although the strength of these findings is confounded by ASCT and cumulative bortezomib dose received, KP1 data is consistent with findings from the large phase III UPFRONT study which showed no difference in PFS between VD (doublet), VTD (triplet) and VMP (triplet), (14.7 vs. 15.4 vs. 17.3 months, respectively) (Niesvizky et al 2015).

The impact on local practice in TVCN has been large, as described in the testimonial (Appendix 2). In clinical practice, as a result of this work, clinicians continue bortezomib therapy for the maximum number of doses allowed by NICE, and do not discontinue therapy early when maximum response is achieved. Also, we tend to use more triplets because this was associated with a trend for better outcomes, despite the lack of statistical significance.

3.2. Improving carfilzomib outcomes:

3.2.1. Literature review and rationale of study:

Carfilzomib is a proteasome inhibitor, NICE-approved in 2017 to treat myeloma at first relapse (NICE 2017), as a result of data from ENDEAVOR trial which demonstrated improved median PFS of carfilzomib plus dexamethasone (CarDex) given twice-weekly, compared to bortezomib with dexamethasone (18.7 months vs. 9.4 months, p<0·0001) (Dimopoulos et al 2016).

However, carfilzomib showed high cardiovascular adverse events (CVAEs): hypertension (G1-2: 16%; ≥G3: 9%), cardiac failure (CF; G1-2: 3%; ≥G3: 4.8%) and ischaemic heart disease (G1-2: 0.9%; ≥G3: 1.7 %), (Dimopoulos et al 2016). Another trial (ARROW) investigated once weekly (70mg/m^2) vs. twice-weekly (27mg/m^2) dosing of carfilzomib (Moreau et al 2018). Median PFS was statistically in favour of once weekly carfilzomib (11.2 vs 7.6 months; p=0.0029). However, ≥G3 AEs we observed in 68% and 62% of patients in the once vs twice-weekly arms, respectively (Moreau et al 2018).

In view of the safety and efficacy data reported in ENDEAVOR and ARROW, carfilzomib dosing and frequency need to be further optimised. The European Myeloma Network (EMN) published a guidance document about the prevention, monitoring and management of cardiac toxicities induced by carfilzomib (Bringhen et al 2019).

Myeloma clinicians need to further understand the tolerability and efficacy outcomes of this novel agent in the real-world, where patients often present with advanced age and/or co-morbidities, and are under-represented in the large phase 3 trials.

In view of lack of real-world data on this subject, we conducted a study to investigate carfilzomib dosing, efficacy and toxicity outcomes in a cohort of myeloma patients treated with CarDex at first relapse, to understand outcomes of this therapy in the real-world and identify safe and efficacious dosing strategies. I designed and led this collaborative work for a period of 22 months (July 2017 to April 2019).

This work was published in the British Journal of Haematology and the paper will be referred to herein as key publication 2 (KP2).

3.2.2. Methodology:

The study was approved by the regional Oxford University Hospitals NHS Foundation Trust across all TVCN participating sites. I collected data on a number of patient, disease and treatment characteristics for a total of 30 patients. In particular, KP2 focused on highlighting history of pre-existing cardiac morbidities because there is a need to establish if carfilzomib can still be safely administered to some of those patients in the real-world; something that the main phase 3 carfilzomib trials did not investigate (KP2).

Two main efficacy outcomes were evaluated: response rates and time to best response. I did not attempt to produce PFS and OS curves because the follow-up period was too short for survival analysis of subgroups. In view of the current concerns of cardiovascular AEs of carfilzomib, it was important to review carfilzomib dosing schedules (full twice-weekly dosing or attenuated once weekly dosing), treatment duration and dose reductions/discontinuations (KP2).

On reflection from my clinical practice as an independent prescriber in Oxford's myeloma clinic and following on from discussions with fellow myeloma researchers across the UK, I looked at relative dose intensity (RDI) as an additional outcome measure, which has not been done before, and would be useful for clinicians in clinical practice (KP2).

On reflection from KP1 where there was a lack of AE data analysis, KP2 focused on understanding all grade AEs, particularly cardiovascular AEs. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used to collect data on AEs attributed to carfilzomib therapy (KP2).

3.2.3. Key results:

Out of a total of 30 patients eligible for inclusion, this real-world study identified 13 patients (43·3%) presenting with at least one pre-existing cardiac morbidity, of whom 10 had hypertension (KP2).

The overall response rate (ORR) was 92·6% (25/27). Median time to best response was 75 days (range 30–210), i.e. after two to three cycles. This is very useful for clinicians and patients to be aware of, in order to manage treatment expectations (KP2).

KP2 identified variability in dosing across the cohort. Five patients received full twice-weekly dosing throughout, and six were dose-reduced to weekly from the beginning. The remainder of the cohort (19/30 = 63·3%) received full dosing (56mg/m^2 as per ENDEAVOR trial) for a number of cycles (1–12) and were then dose-reduced (to either 42 or 36 or 27 mg/m^2) or frequency-reduced to weekly instead of twice weekly, or both (KP2). Main reasons for dose reductions were infections, hypertension, dyspnea, chest pain, history of GI perforation, fatigue, increase in baseline creatinine by nearly 50%, and diagnosis with a pulmonary embolism. Median RDI for the total cohort throughout the follow-up period was 67·4% (range: 26·6–100%) (KP2).

Of a total of 60 AEs in the cohort (fully reported in the published paper), 16 were ≥G3, of which the most frequent were: anaemia, infections, hypertension, and PE. Of the 7 incidences of all grade hypertension, 4 were worsening pre-existing hypertension (G1-2) and 3 were new (one G2 and two G3) (KP2).

3.2.4. Impact of my research and future directions:

This study was the first to report real-world outcomes of carfilzomib in the UK. To my knowledge, there are no published UK data describing myeloma outcomes in this particular setting. KP2 demonstrated that carfilzomib in the real-world is an efficacious therapy, and resulted in a high ORR. KP2 also showed that carfilzomib has a reasonably good tolerability profile (total of 16 AEs of ≥G3) with a median relative dose intensity of 67.4%. For instance, ≥G3 thrombocytopenia in this cohort was comparable to ENDEAVOR trial (10% vs. 8·4%), in addition to ≥G3 anaemia (13·3% vs. 14·5%), and ≥G3 hypertension (6·7% vs. 9%) (KP2). Moreover, KP2 demonstrated that caution should be applied in patients with cardiac co-morbidities, but the latter should not be a reason to exclude carfilzomib as a treatment option. However, and as per recent EMN guideline, risk assessment, comprehensive ongoing monitoring and proactive management of toxicities (with dose interruptions or delays or reductions) are required (KP2). The impact on local practice was observed across TVCN, soon after the dissemination of these results at the regional "Update in Myeloma" evening. As described in the testimonial (Appendix 2), carfilzomib is now used more often, with caution but with more confidence since this data was published. Frequency of carfilzomib is reduced upfront if patients have a pre-existing cardiac morbidity or advanced age.

3.3. Improving outcomes of DPACE-based therapy:

3.3.1. Literature review and rationale of study:

Despite a significantly improved availability of novel agents to treat myeloma in the UK and the constantly changing myeloma therapeutic paradigm, some patients infrequently present with aggressive myeloma where the immediate use of novel agents is not the best option to quickly de-bulk the disease.

The use of dexamethasone plus thalidomide in combination with a continuous infusion of cisplatin, doxorubicin, cyclophosphamide, and etoposide (DTPACE) is appropriate for those patients. It was first described in the relapsed setting and showed effectiveness as induction therapy before ASCT (Lee et al 2003). This intensive therapy is administered in hospital as an inpatient, where patients are admitted for a period of at least 5 days, and where cytotoxic chemotherapy is administered slowly but continuously over a period of 4 days in order to provide an optimal area under the curve (AUC) to maximally target myeloma cells, and also to reduce the risk of cardiotoxicity from doxorubicin. It is, however, associated with a high incidence of G3/4 toxicities.

The addition of bortezomib to DTPACE (VTDPACE) led to improved outcomes (Barlogie et al 2007; Lakshman et al 2018). Historical indications for DPACE-based therapies include salvage treatment of aggressive MM, plasma cell leukaemia, and initial presentation with extra-medullary disease. Infusional chemotherapy continues to play a role, especially as a bridge to ASCT or as a method of rapid tumour de-bulking (Yuen et al 2018).

In the UK and in the era of novel therapies, variability in clinical decision-making amongst myeloma clinicians working at different hospitals led to the non-uniformity of UK practice regarding the use of DPACE-based chemotherapy. Therefore, we conducted a retrospective study in order to assess outcomes of the current indications of this therapy and to identify the optimal role for it within the evolving myeloma treatment landscape. This work was published in the European Journal of Haematology and the paper will be referred to herein as key publication 3 (KP3).

3.3.2. Methodology:

The cohort included patients treated with DTPACE, VTDPACE or VRDPACE from 2009 to 2017. I set out to assess response rates, OS, TTNT for the total cohort and between subgroups, G3/4 haematological toxicities and treatment-related mortality (TRM) (KP3). The

study was approved by the regional Oxford University Hospitals NHS Foundation Trust across all participating sites.

3.3.3. Key results:

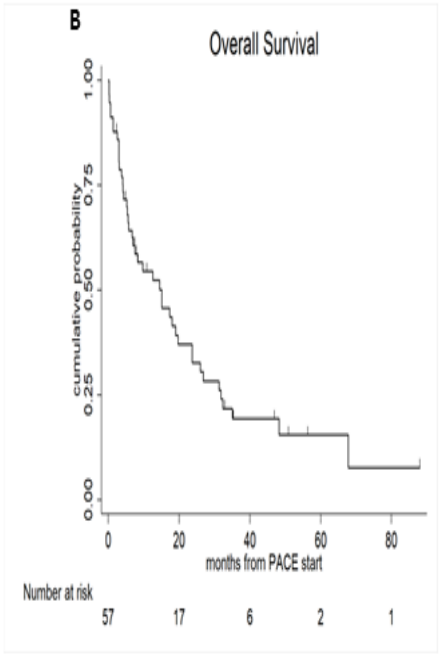
Given the rarity of use of this intensive chemotherapy in myeloma, it was a collaborative effort to find eligible patients making a cohort of 59 patients, which is the largest cohort reported in the UK to date. DPACE was used as 1st line bridging to ASCT in 14 patients, and for relapsed disease in 45 patients. Choice of DPACE therapy was: DTPACE (39%), VTDPACE (35.6%), and VRDPACE (25.4%), Fig 2A. Median number of cycles received was 2 (1-4). ORR was 66.1%: sCR (23.7%), VGPR (11.9%) and PR (30.5%) (KP3).

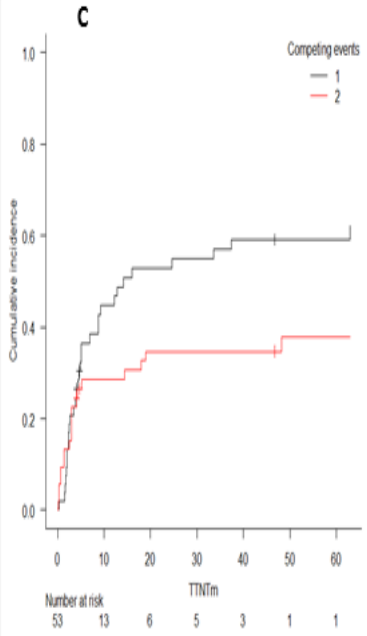
Median OS for the total cohort was 15.1 months, Fig 2B; and median TTNT was 14.2 months, Fig 2C. Median TTNT (ASCT post-DPACE vs. no ASCT) was (12.8 vs. 2.7 months, p=0.118), Fig 2D. Median TTNT (months) according to number of prior therapies was (>2: 5.1 vs. ≤2: 24.6, p=0.34), Fig 2E (KP3).

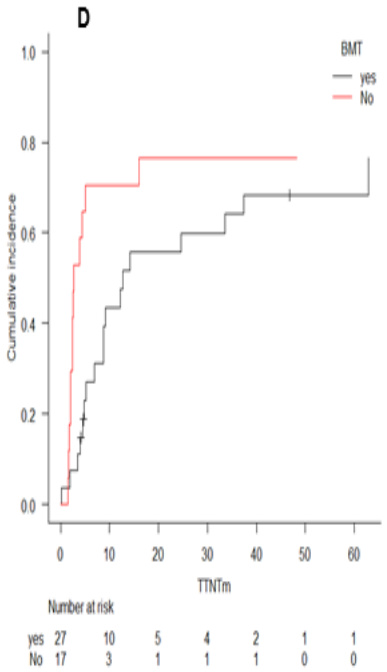
After cycles 1 and 2 respectively, 49.1% and 40.7% of patients experienced at least one G3-4 haematological toxicity; 64.4% and 44.1% required red blood cell (RBC) or platelet support. TRM rate was 10.5% (KP3).

A

Characteristic	Total patient cohort (n=59)
Age (years):	
≤ 50	17 (28.8%)
51-64	35 (59.3%)
≥ 65	7 (11.9%)
Sex	
Male	36 (61%)
Female	23 (39%)
Myeloma subtype	
Ig MM	45 (76.3%)
Light chain MM	9 (15.2%)
Non-secretory MM	3 (5.1%)
Plasma cell leukaemia	2 (3.4%)
ISS staging	
I	15 (25.4%)
II	16 (27.1%)
III	18 (30.5%)
unknown	10 (17%)
Number of adverse cytogenetics	
0	6 (10.2%)
1	18 (30.5%)
≥2	7 (11.9%)
unknown	28 (47.5%)
Prior therapies	
IMiD-based	4 (6.8%)
PI-based	6 (10.2%)
IMiD+PI-based	43 (72.9%)
Chemo-based	1 (1.7%)
None	5 (8.5%)
Prior ASCT	
Yes	27 (45.8%)
No	32 (54.2%)
Choice of DPACE therapy:	
DTPACE	23 (39%)
VTDPACE	21 (35.6%)
VRDPACE	15 (25.4%)
Number of DPACE cycles:	
Median (range)	2 (1-4)







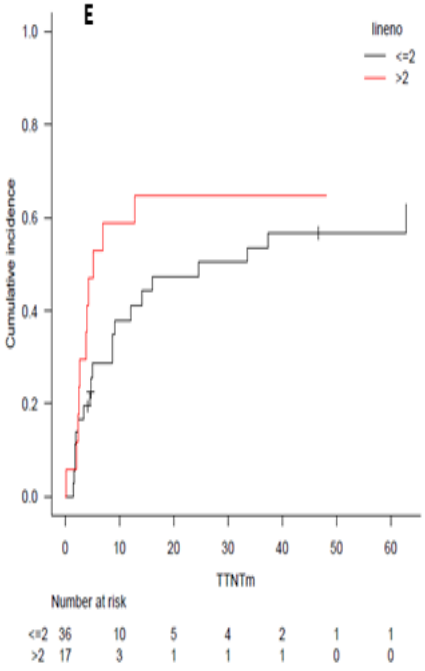


Figure 2: A) Patient, disease and treatment characteristics, B) Overall survival (OS) in the total cohort, C) TTNT, D) TTNT (ASCT post-DPACE vs. no ASCT), E)TTNT according to number of prior therapies. This figure is obtained from Figure 1 of (Djebbari et al 2020, EJH) following approval and permission received from John Wiley and Sons and Copyright Clearance Center (https://s100.copyright.com/CustomerAdmin/PLF.jsp?ref=332737d9-d832-453f-93c4-6dca1b1d348d)

3.3.4. Impact of my research, and future directions:

This was the largest UK real-world analysis of DPACE therapy in myeloma. It showed that TRM rate was consistent with a study of 65 DCEP patients (10.5% vs. 9.7%) (Yuen et al 2018). KP3 also demonstrated that DPACE can benefit patients by prolonging TTNT, only if consolidated with an ASCT afterwards. On the other hand, it had limited benefit in non-ASCT-eligible patients, or those more heavily pre-treated (KP3).

The impact of this work on local practice in TVCN and across the UK was notable, and is documented in the testimonial (Appendix 2). This study changed practice and re-defined the subgroup of patients who benefit the most from this therapy. For patients who are non-ASCT-eligible, results from KP3 suggest to consider scheduling a subsequent therapy shortly post-DPACE, to maintain the achieved response or extend its duration, subject to tolerability and fitness for further treatment (KP3).

My data proved that DPACE still has a place in the continuously changing myeloma treatment algorithms. This work helped to rationalise the use of this intensive therapy, and focus it on bridging to ASCT, or in relapsed disease which is not heavily pre-treated. Its use in any other settings has reduced.

4. OPTIMISING MYELOMA TREATMENT STRATEGIES:

4.1. Continuous versus fixed-duration therapy:

4.1.1. Literature review and rationale of study

Prior to the novel agent era, treatment for TNE NDMM consisted of melphalan and prednisone (MP) given as fixed-duration therapy (FDT) followed by a treatment-free interval (TFI) until disease relapse.

Today, standards of care in the UK consist of FDT using either a thalidomide-containing regimen in combination with an alkylating agent and a steroid, for instance: melphalan, prednisone, and thalidomide (MPT) or cyclophosphamide, thalidomide, and dexamethasone (CTD) or a bortezomib-containing regimen, i.e. bortezomib, melphalan, and prednisone (VMP) (NICE 2011) Despite improved outcomes with FDT regimens, several studies have evaluated the impact of continuous and maintenance treatment approaches in both the TE and TNE NDMM settings.

Lenalidomide, an oral derivative of thalidomide, has a different toxicity profile compared to its parent drug (SPC 2019). In the FIRST trial (Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide, MM-020), PFS and OS were significantly longer in TNE NDMM patients treated with lenalidomide and low-dose dexamethasone until disease progression (Rd continuous) compared with those treated with MPT given for a fixed duration of 72 weeks (Benboubker et al 2014). In addition, rates of G3-4 neutropenia, sensory PN were lower, and HRQoL related to treatment AEs was significantly better with Rd continuous compared with MPT (Benboubker et al 2014; Facon et al 2018).

In UK clinical practice, CTD and bortezomib-based combinations, including VMP, are used more widely than MPT as FDT in patients with TNE NDMM. Therefore, it is important to understand how Rd continuous treatment compares with the outcomes of patients with TNE NDMM in the UK real-world setting.

As such, we conducted a case-matching TVCN-wide study in the TNE NDMM setting to compare outcomes of FDT, which is reflective of UK clinical practice, with those of Rd continuous from the MM-020 trial. This work was published in Leukemia & Lymphoma and the paper will be referred to herein as key publication 4 (KP4).

4.1.2. Methodology:

This large study was conducted in collaboration with Celgene (a leading pharmaceutical company in malignant haematology, and manufacturer of lenalidomide) to compare efficacy outcomes of FDT (UK standard of care) with the continuous Rd arm of the FIRST trial, in the TNE NDMM setting (KP4). The study was approved by the regional Oxford University Hospitals NHS Foundation Trust across all participating sites.

To facilitate this comparison, case-matching and random sampling (according to 2 important prognostic factors for survival: age: ≤ 75 vs. > 75 years, and ISS Staging: I or II vs. III) were used to proportionally match a group of patients in the continuous Rd arm of FIRST trial to patients in the FDT cohort. The FDT cohort and the age- and ISS-matched Rd continuous cohort comprised 223 and 254 patients, respectively Fig 3 (KP4).

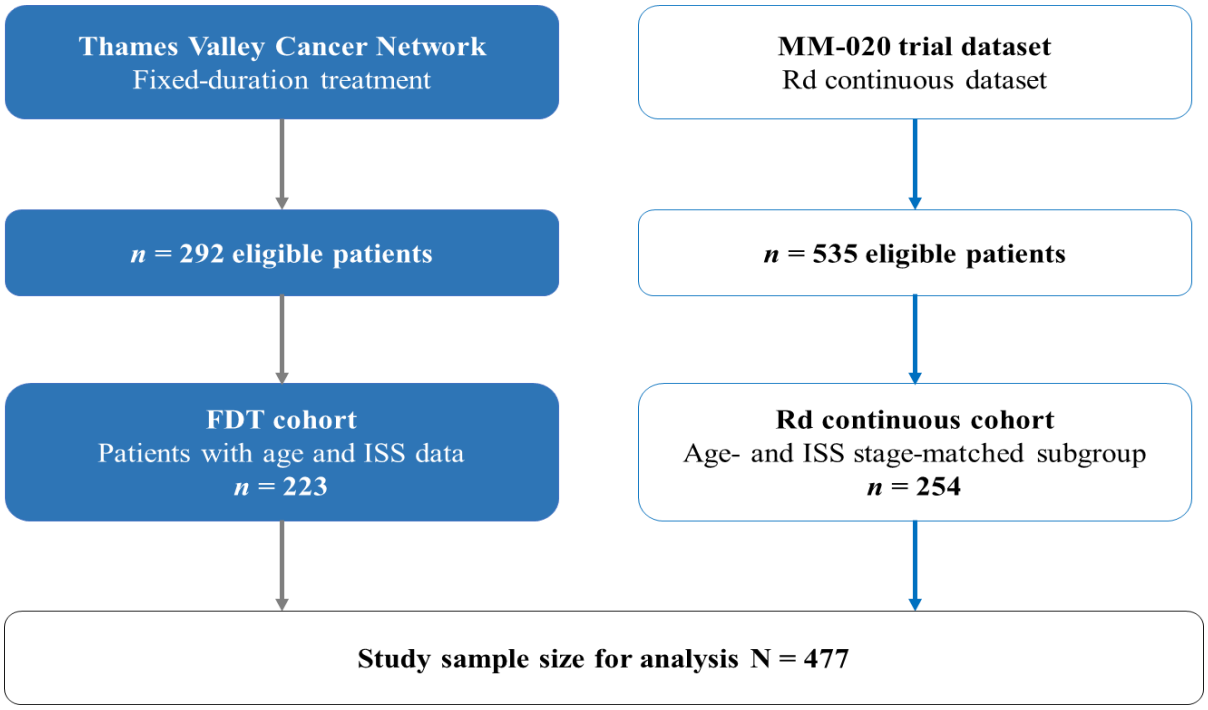


Figure (3): Age- and ISS-matched FDT and Rd continuous cohorts (KP4). This figure is obtained from Figure 1S of (Sharpley et al 2020, Leukemia & Lymphoma) under the Creative Commons CC-BY-NC-ND license (https://creativecommons.org/licenses/), and following permission obtained from Taylor and Francis Online (https://www.tandfonline.com/)

On reflection from my KP1, in which two main survival outcomes of bortezomib-based therapies (OS, and TTNT) were evaluated; it was important to investigate PFS as a 3rd

survival outcome in this study because it is a standard endpoint in phase 3 myeloma trials (KP4).

4.1.3. Key results

Study cohorts were: FDT (n=223) and Rd continuous cohort (n=254) (KP4). Median number of cycles received was 6 (range 1–28) in the FDT cohort and 19 (range 1–91) in the Rd continuous cohort. The most common frontline therapies in the FDT cohort were thalidomide-based regimens (66%) with a mean thalidomide daily dose of 51.4mg, and proteasome inhibitor-based regimens (24%) with a mean cumulative dose of bortezomib of 4mg/m^2 per cycle (KP4).

This study demonstrated that the median OS with FDT was statistically inferior to Rd continuous: 30.3 vs. 58.6 months, HR 0.54, $P < 0.0001$) Fig (4A). Median PFS with FDT was also statistically inferior to Rd continuous (9.0 vs. 25.7, HR 0.37, $P < 0.0001$) Fig (4B). In the same way, this study demonstrated inferior median TTNT with FDT compared to Rd continuous (16.7 vs. 42.2, HR 0.38, $P < 0.0001$), Fig (4C) (KP4).

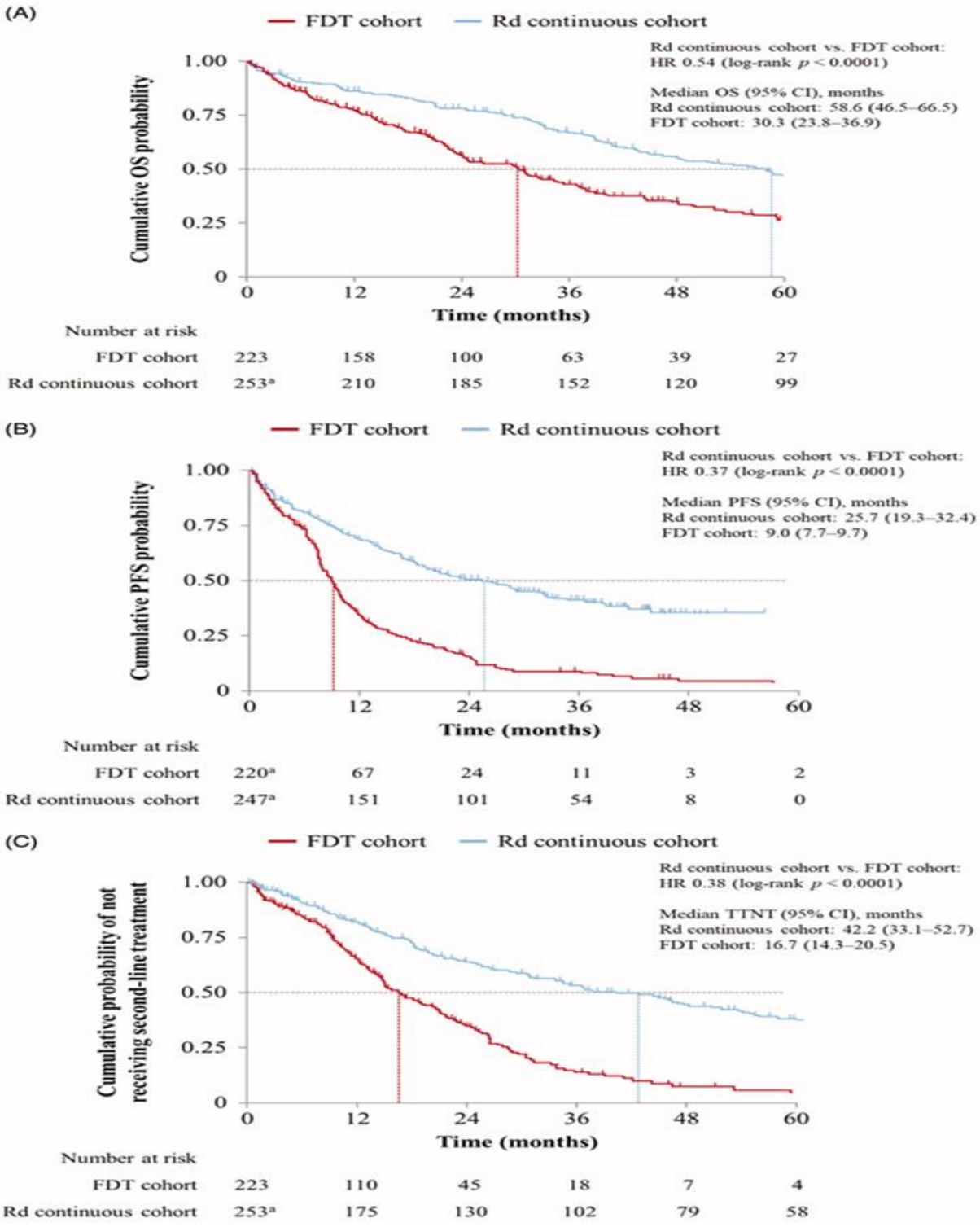


Figure (4): Comparison of survival outcomes (FDT vs. Rd continuous): A) OS, B) PFS, C) TTNT (KP4). This figure is obtained from Figure 1 of (Sharpley et al 2020, Leukemia & Lymphoma) and was used under the Creative Commons CC-BY-NC-ND license (https://creativecommons.org/licenses/), and following permission obtained from Taylor and Francis Online (https://www.tandfonline.com/)

4.1.4. Impact of my research, and future directions:

This study demonstrated that using FDT strategy in the elderly TNE NDMM setting confers inferior OS, PFS, and TTNT than their age- and ISS-matched counterparts who were treated with Rd continuous treatment as part of the MM-020 trial (KP4). This data is consistent with other published studies that reported the benefits of continuous therapy in this setting (Palumbo et al 2014; Palumbo et al 2012).

KP4 results were particularly supportive of the continuous therapy strategy for these patients, and added to the body of evidence because we performed a comparison of Rd continuous to UK-based FDT therapies (e.g. thalidomide-based: CTD, CTDa, and bortezomib-based: VD), which has not been done in the FIRST trial (only compared Rd continuous to thalidomide-based MPT therapy) (Benboubker et al 2014).

Since the completion of this work, NICE submission by Celgene for continuous lenalidomide plus dexamethasone in the TNE NDMM setting was successful, and this therapy has become available in the UK from June 2019 (NICE 2019). This offers patients and clinicians an additional treatment choice to use as frontline therapy, which is both safe and efficacious

The work had a significant impact locally and nationally. Internationally, it was first presented at the American Society of Haematology (ASH) Conference in 2017, then at the European Haematology Association (EHA) Conference in 2018.

4.2. Treatment-free interval as a measure of efficacy:

4.2.1. Literature review and rationale of study

Up to 45% of new MM diagnoses in the UK are made in patients aged ≥75. Objectives of first-line treatment in elderly patients are disease control whilst maintaining HRQoL, which translates into improved survival (Mateos et al 2017).

As the myeloma treatment landscape continues to be shaped, continuous therapy in the TNE NDMM setting has become the new standard of care. PFS advantage of continuous Rd was demonstrated in the MM015 trial and the FIRST trial (Benboubker et al 2014; Palumbo et al 2014). Survival advantages of continuous daratumumab with VMP (D-VMP) and of continuous daratumumab with Rd (D-Rd) were recently demonstrated in ALCYONE and MAIA trials, respectively (Mateos et al 2018; Facon et al 2019).

However, the decision to employ a continuous first-line strategy in routine practice requires a careful assessment of patients. Achieving optimal outcomes in NDMM patients aged over 75 years remains a considerable challenge for the myeloma community because of frailty and/or co-morbidities (Zweegman et al 2017).

TFI in routine practice can occur if physicians and patients jointly decide to use FDT strategy and discontinue therapy after 4-8 cycles based on myeloma response achieved. Therapy can also be discontinued early as a result of significant toxicities. In both scenarios, TFI becomes very important for patients because it allows them to recover from toxicities and to restore a good QoL (KP5). TFI and good HRQoL have been described as additional measures of efficacy which can be employed to make individualised treatment decisions. A UK cross-sectional survey of 370 myeloma patients demonstrated that being in a first TFI and experiencing a longer TFI were significantly associated with a better HRQL (Acaster et al 2013).

Before NICE approved continuous Rd in the TNE NDMM setting (NICE, 2019), FDT was the only standard of care with either a bortezomib-based or a thalidomide-based regimen, and remains a current option if lenalidomide is inappropriate.

In view of the importance of TFI in the real-world, I conducted a large retrospective study to evaluate TFI as an additional metric of efficacy in routine practice, after 1st and subsequent lines of therapy in elderly NDMM patients. The aim was to understand current practice and

identify strategies which can increase TFI and improve future outcomes. This work was published in PLOS One and the paper will be referred to herein as key publication 5 (KP5).

4.2.2. Methodology:

In a cohort of 292 patients, we set out to quantify TFI as a primary endpoint, after 1st and subsequent lines of therapy in the total cohort and in the following subgroups: according to age (≤75 vs. >75 years) and co-morbidities as per Charlson Co-morbidity Index (CCI) score: (CCI: 0-2) vs. (CCI: 3-4) vs (CCI: ≥5) (KP5). The study was approved by the regional Oxford University Hospitals NHS Foundation Trust across all participating sites.

I originally presented this data at the Annual American Society for Haematology (ASH) Conference in Dec 2017, during which I compared outcomes based on age and choice of first line therapy (bortezomib vs. thalidomide). I had discussions with a number of international collaborators and fed back to my research group in Oxford that it would more useful for the myeloma community to evaluate the influence of co-morbidities on outcomes instead of therapy choice.

On reflection from this feedback, we decided to conduct further extensive work to collect co-morbidity data, and perform further analyses of TFI and survival outcomes according to CCI. This resulted in stronger data and a more valuable research paper (KP5).

4.2.3. Key results:

The older cohort (>75 years) had a higher proportion of moderately to severely co-morbid patients compared to those ≤75 years (60% vs. 39%). Thalidomide was the most commonly used 1st line therapy (61%), followed by bortezomib-based (22%), alkylator-based (10%), and lenalidomide (7%). The mean number of treatment cycles (6) was comparable between subgroups (KP5).

Results in KP5 demonstrated that median TFI in the total cohort was longest after 1st line therapy at 6.9 months, Fig (5A), and reduced after 2nd line therapy to 1.8 months and after 3rd line therapy to 0.6 months. KP5 also showed that, in both age subgroups, TFI was also longest after 1st line therapy, and decreased with increasing lines of therapy. In all co-morbidity subgroups (CCI: 0-2, 3-4 and ≥5), TFI followed the same trend (KP5).

KP5 showed that older age (>75 years) confers significantly inferior OS (P<0.0001) Fig (5B), and PFS (P<0.01), Fig (5C), compared to ≤75 years. Patients experienced worse OS (P=0.01), Fig (5D), and worse PFS (p=0.025), Fig (5E), with increasing CCI scores (KP5).

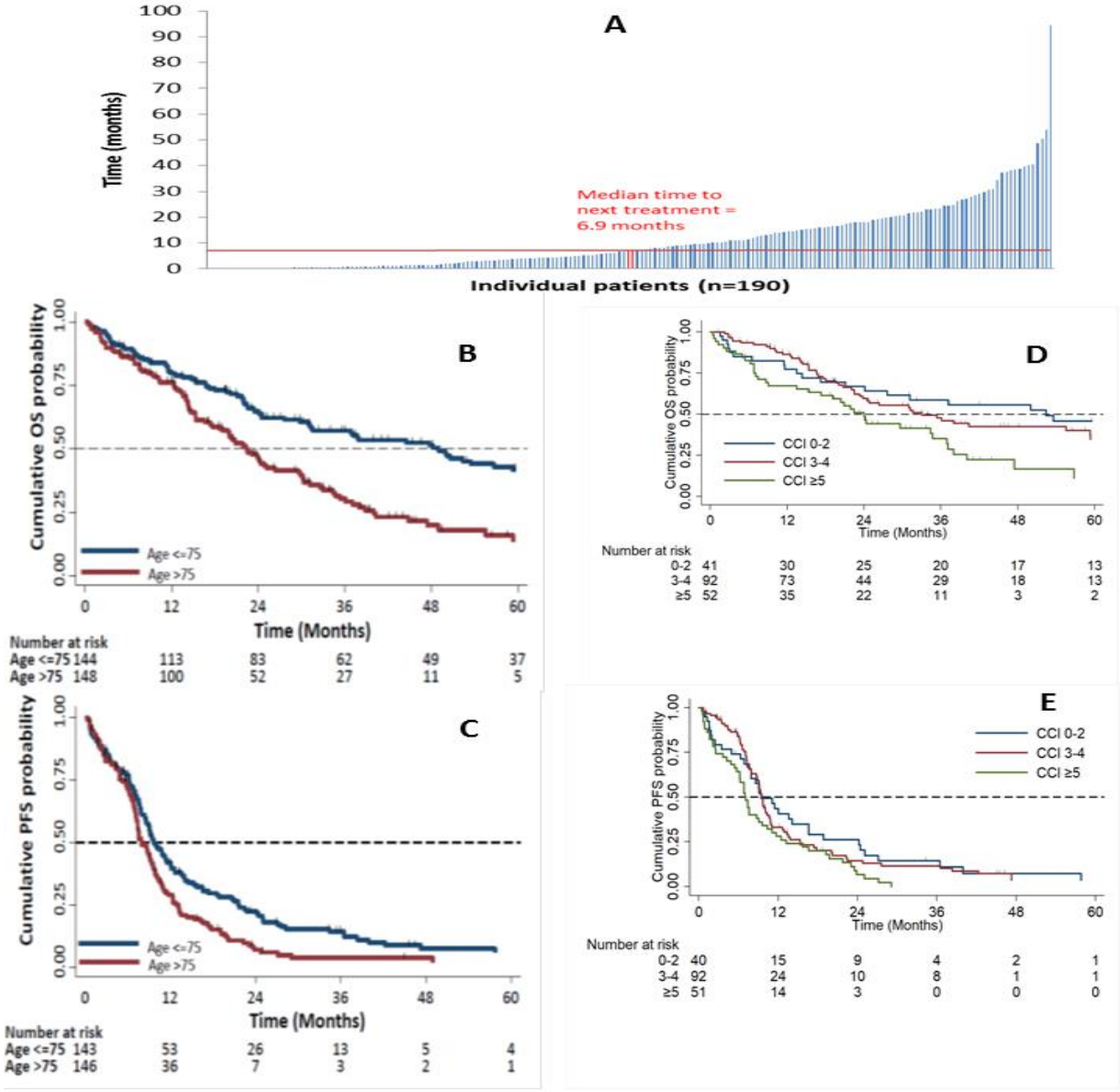


Figure (5): Treatment free interval and survival outcome: A) Waterfall plot of TFI following first-line therapy, B) OS by age (>75 vs. ≤75 years), C) PFS by age, D) OS by CCI (mild (0-2) vs. moderate (3-4) vs. severe (≥5)), E) PFS by CCI, (KP5). This figure is adapted from Figures 1,4,5,6,7 of (Djebbari et al 2020, PLOS ONE) under the open access license "CC-BY" (https://journals.plos.org/plosone/s/licenses-and-copyright). The publisher confirms that no further permissions are required.

4.2.4. Impact of my research, and future directions:

This was the first and largest UK study to investigate TFI exclusively in the real-world elderly TNE NDMM setting, because this endpoint is yet to be adequately quantified, and appears to be of value to patients (KP5).

This study demonstrated that median TFI in the total cohort was 6.9 months and declined with subsequent treatment phases. These results are consistent with data from a large international real-world study of myeloma patients, which showed that median TFI and time to progression decrease with increasing lines of therapy (Yong et al 2016).

KP5 also demonstrated that a FDT approach for patients >75 years confers inferior PFS and OS compared to patients ≤75 years (KP5). This data is consistent with a number of subgroup analyses from large phase 3 trials in the TNE NDMM setting, such as FIRST, VISTA and ALCYONE trial (San Miguel et al 2008; Benboubker et al 2014; Mateos et al 2018).

In addition, KP5 showed that survival outcomes shorten with increasing co-morbidity burden. This data is in line with a retrospective Japanese study which demonstrated that comorbidity burden and PS were predictive of outcomes in a cohort of patients ≥80 years of age (Matsue et al 2016).

My work suggests that, where continuous therapy is not appropriate due to toxicities or patient choice, an effective FDT combination with good tolerability should be considered as a reasonable alternative approach, provided it contains novel agents (not limited to thalidomide or bortezomib). Future management can also consider possibly stopping lenalidomide after 18 cycles if appropriate, because FIRST trial showed no OS benefit between continuous Rd and 18 cycles of Rd (Benboubker et al 2014).

Another key message from KP5 was: where a decision is made to use FDT instead of continuous therapy, the aim of therapy besides improving survival should be to maximise TFI which can, in turn, help improve HRQoL. The length of the resultant TFI from each therapy (until a myeloma relapse) should be viewed at as an additional indicator by which we can assess efficacy. As such, the title of paper was “TFI as an additional measure of efficacy” (KP5).

The impact of my work on clinical practice, as described in the testimonial (Appendix 2) was to prompt clinicians to engage patients in the decision-making about continuous therapy

versus FDT which includes TFI. In order to help manage treatment expectations from clinicians and patients, this study quantified TFI and demonstrated that this efficacy endpoint is longest after 1st line therapy, and declines significantly following subsequent lines of therapy; this is a useful data for NDMM patients who would prefer to opt for the FDT strategy followed by a TFI. In the relapsed setting, however, patients and clinicians may decide to opt for the continuous therapy strategy over FDT because TFI was shown to be very short with subsequent lines of therapy (KP5).

5. IMPROVING TOLERABILITY OF MYELOMA THERAPIES:

5.1. Optimising dosing of oral myeloma therapies to improve tolerability:

5.1.1. Literature review and rationale of study

Some oral systemic anticancer therapies (SACT) are administered daily and continuously until disease progression or unacceptable toxicity (e.g. imatinib), and other agents are administered on specific days of a cycle followed by a break (e.g. lenalidomide), and some are administered for a specific number of treatment cycles then discontinued thereafter (e.g. thalidomide) (BNF, 2017). Oral SACT can be associated with high-grade toxicities leading to dose interruption/delay, or treatment discontinuation. These AEs can also adversely affect HRQoL; treatment interruption or discontinuation may reduce treatment efficacy.

One approach to maintain patients on continuous oral SACT is to use non-standard dosing, where unlicensed doses/schedules are employed to improve tolerability, maintain HRQoL and continue therapy. This approach can be particularly useful for elderly and co-morbid myeloma patients taking oral agents such as: thalidomide, lenalidomide, pomalidomide, ixazomib or panobinostat. Official guidance on non-standard oral SACT dosing is non-existent, and there is currently a gap in the literature on this subject.

Therefore, I conducted a large systematic review to identify evidence of, and outcomes (efficacy, toxicity, HRQoL) from non-standard dosing of oral SACT in oncology and malignant haematology, in order to inform prescribing practices. In particular, it was important to identify the evidence in myeloma.

Due to the enormity of this task, this work was published as two separate papers: the methodological protocol in the journal Systematic Reviews, and the findings in the journal BMC Cancer, which will be referred to herein as key publications 6 (KP6) and 7 (KP7), respectively.

5.1.2. Methodology:

This large systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines (Moher et al 2015) to identify evidence of non-standard dosing of oral SACT in cancer. It was registered on the PROSPERO database with the following ID: CRD42017076195 (KP6).

Prior to conducting this review, I identified a gap in my learning as a junior researcher, and established the need to allocate time and resources to gain a good understanding of this research method. In July 2017, I enrolled in a week-long face-to-face systematic review course run by the University of Oxford, in which I learnt research methods used to design and conduct a systematic review, and how to report my findings.

We intended for this piece of work to be very comprehensive, and to benefit not only myeloma clinical practice, but all tumor groups in oncology and malignant haematology However, I still had myeloma studies at heart and I was confident outcomes from the myeloma studies can be described separately, and findings can be shared with the myeloma community.

A comprehensive search of 78 different oral SACT was performed in MEDLINE®, Embase®, Cochrane Library©, and Cumulative Index to Nursing and Allied Health Literature (CINAHL©) databases (KP6), followed by search expansion. The method is fully described in KP6. The authors worked together very closely to screen results, and appraise the quality of included studies, Fig (6) (KP7).

As expected, this review was large, and identified 34 studies eligible for inclusion, of which 2 were myeloma papers. I reported the findings in KP7, which discussed evidence of non-standard dosing for all oral SACT drugs in the BNF, including myeloma drugs.

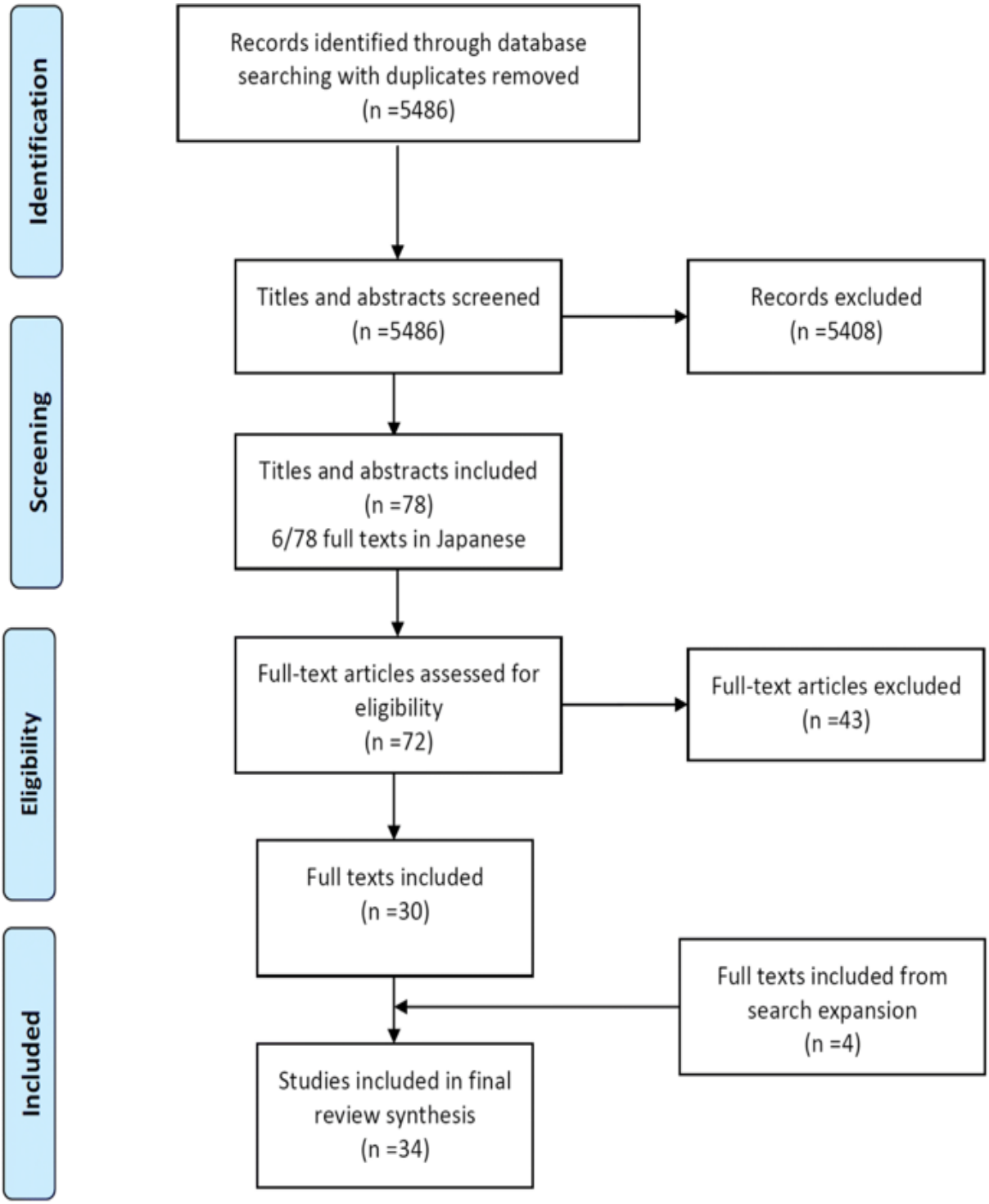


Figure (6): Flow diagram of search strategy and inclusion/exclusion (KP7). This figure is obtained from Figure 1 of (Djebbari et al 2018, BMC Cancer) under the Creative Commons Attribution license "CC-BY" (https://www.biomedcentral.com/about/policies/reprints-and-permissions). The publisher confirms that no further permissions are required.

5.1.3. Key results:

Of 5486 search results, 34 studies were eligible for inclusion, describing non-conventional dosing of oral SACT in oncology and in malignant haematology. Four studies were late phase clinical trials, 15 were cohort studies and 15 were case reports (KP7).

The number of studies per drug investigated was as follows: sunitinib (10), imatinib (7), sorafenib (2), vemurafenib (3), dasatinib (2), lenalidomide (2), crizotinib (2), erlotinib (2), gefitinib (2), temozolomide (1) and thalidomide (1). Dose interruption strategies were the most common (14 studies), followed by dose reductions (9 studies), and other dosing strategies (11 studies) (KP7).

Of all 34 studies, two reported non-standard dosing in myeloma: one of thalidomide and of lenalidomide (KP7).

The thalidomide study was a small randomised trial of 23 myeloma patients, and investigated efficacy and AEs of a one-week interruption of thalidomide following daily administration for 3 weeks, compared to continuous therapy (Mangiacavalli et al 2012). The study was rated of a (moderate to high) quality. The study reported worse OS ($p < 0.001$) and PFS ($p = 0.02$) in the intermittent arm compared to the continuous arm. However, there was no difference in peripheral neuropathy (PN). A drawback of this study was the very small number of patients ($\leq$30) (Mangiacavalli et al 2012).

The lenalidomide study was a small prospective single arm myeloma cohort study. It aimed to evaluate efficacy and cost-saving of alternate-day dosing of lenalidomide (25mg every other day for 21 days then 1 week break) (Popat et al 2014). The study was rated of a (moderate to low) quality. Median duration was 12 cycles. Median PFS and OS were 11.5 months and 36.5 months, respectively. Cost-savings were £19,408.43 per patient compared to standard daily dosing (Popat et al 2014). A Drawback of the study was the lack of toxicity and HRQoL data. Authors of this paper suggest exploring this strategy in a larger cohort of patients.

5.1.4. Impact of my research, and future directions:

I demonstrated my commitment to go to great lengths to identify much needed evidence of non-standard dosing of all oral SACT (78 agents as of 2017) used in oncology and non-malignant haematology (KP6, KP7). This is very helpful to all cancer clinicians (Oncologists and Haematologists alike) who will inevitably face scenarios in daily practice where non-standard prescribing is the only remaining option, prior to permanently discontinuing therapy due to intolerable toxicities.

I demonstrated acquisition of good research skills by conducting this large piece work, particularly using a robust methodology (KP6). In addition, I demonstrated my ability to appraise and synthesise findings of this work, which was published as a separate paper in BMC Cancer (KP7).

KP6 and KP7 describe the first comprehensive systematic review to tackle this question for all oral anti-cancer agents. Two thirds of all included studies related to solid tumors, whilst only a third discussed haematological malignancies (KP7).

The primary objective of this systematic review was fully met, by identifying and categorising key non-standard dosing strategies, which were: dose reductions, dose interruptions and others (e.g. alternate day dosing).

In terms of drugs used to treat myeloma, we found limited evidence of non-standard dosing (one small sample size clinical trial of thalidomide, and one small prospective lenalidomide cohort study). Limitations of these studies do not allow generalisability of results in clinical practice, but warrant further investigation in large late phase prospective clinical trials.

5.2. Infections-related morbidity and clinical predictors:

5.2.1. Literature review and rationale of study:

Infections cause significant morbidity and mortality in myeloma (Augustson et al 2005). The risk is increased by immunoparesis and immunosuppressive therapy (Teh et al 2014). The nature and patterns of infections has evolved over time, because of the continuously changing myeloma treatment paradigm, which uses a range of systemic therapies from distinct pharmacological classes and with different toxicity profiles.

The aim of first line therapy in TNE NDMM patients is to achieve an optimal disease control and to achieve a good HRQoL (Mateos et al 2017). Infections can directly affect HRQoL, and treatment interruptions due to infection-related morbidity can lead to sub-optimal myeloma responses.

Therefore, it is crucial to understand myeloma infections in the real-world in order to reduce the impact of this complex problem on the patient's treatment journey, particularly in view of advanced age or co-morbidities, and also in view of the recent UK approval of continuous lenalidomide in this setting.

We performed a large retrospective real-world study of 200 consecutive TNE NDMM patients treated with UK standard of care (2009-2018) to establish infection morbidity and mortality over a 12 month period from diagnosis, in addition to identifying clinical predictors of infective episodes.

To my knowledge, there are no published UK routine care data investigating all these outcomes and predictors, particularly in elderly co-morbid patients who are largely under-represented in myeloma clinical trials. This work was published in Haematologica and the paper will be referred to herein as key publication 8 (KP8).

5.2.2. Methodology:

A total of 200 consecutive TNE NDMM patients treated with UK standard of care (2009-2018) (KP8) were included. The study was approved by the Oxford University Hospitals NHS Foundation Trust.

Data were collected on a number of infections outcomes over a 12 month period. UVA and MVA analyses were performed to identify patient, disease, and treatment-related factors

associated with increased incidence of all grade infections, incidence of ≥G3 infections, and infection-related hospitalisation (KP8).

5.2.3. Key results:

Over the first 12 months from diagnosis in a total cohort of 200 patients, 116 documented infections were identified, of which 72 were ≥G3. Cumulative incidence of first all grade, and ≥G3 infections were 33% and 22%, respectively. Two-thirds of infections occurred in the first 6 months. Fifty six episodes required a significant inpatient stay (>3 days) (KP8).

Using UVA of cumulative incidence of all grade and high grade infections, KP8 showed that elevated LDH, COPD, and smoking were associated with a significantly higher infection incidence Fig (6A-F). (KP8).

By MVA Poisson regression, elevated baseline LDH and smoking predicted for higher all grade infection rate, whilst receiving a higher number of treatment cycles (≥6) was associated with a reduced infection rate (KP8).

For high grade infections, this study demonstrated that elevated LDH and smoking predicted for a higher risk of infections, whilst receiving a higher number of treatment cycles and achieving a deep haematological response appeared to have a protective effect (KP8).

Elevated LDH and smoking were independently associated with a higher risk of prolonged infection-related hospital admissions, whereas a deep response appeared to have a protective effect (KP8).

The landmark analysis revealed that median OS was shorter for patients who experienced infections in the first 6 months compared to those who did not. This was demonstrable for all grade infections (p=0.0838) as well as high grade infections (p=0.0176) (KP8).

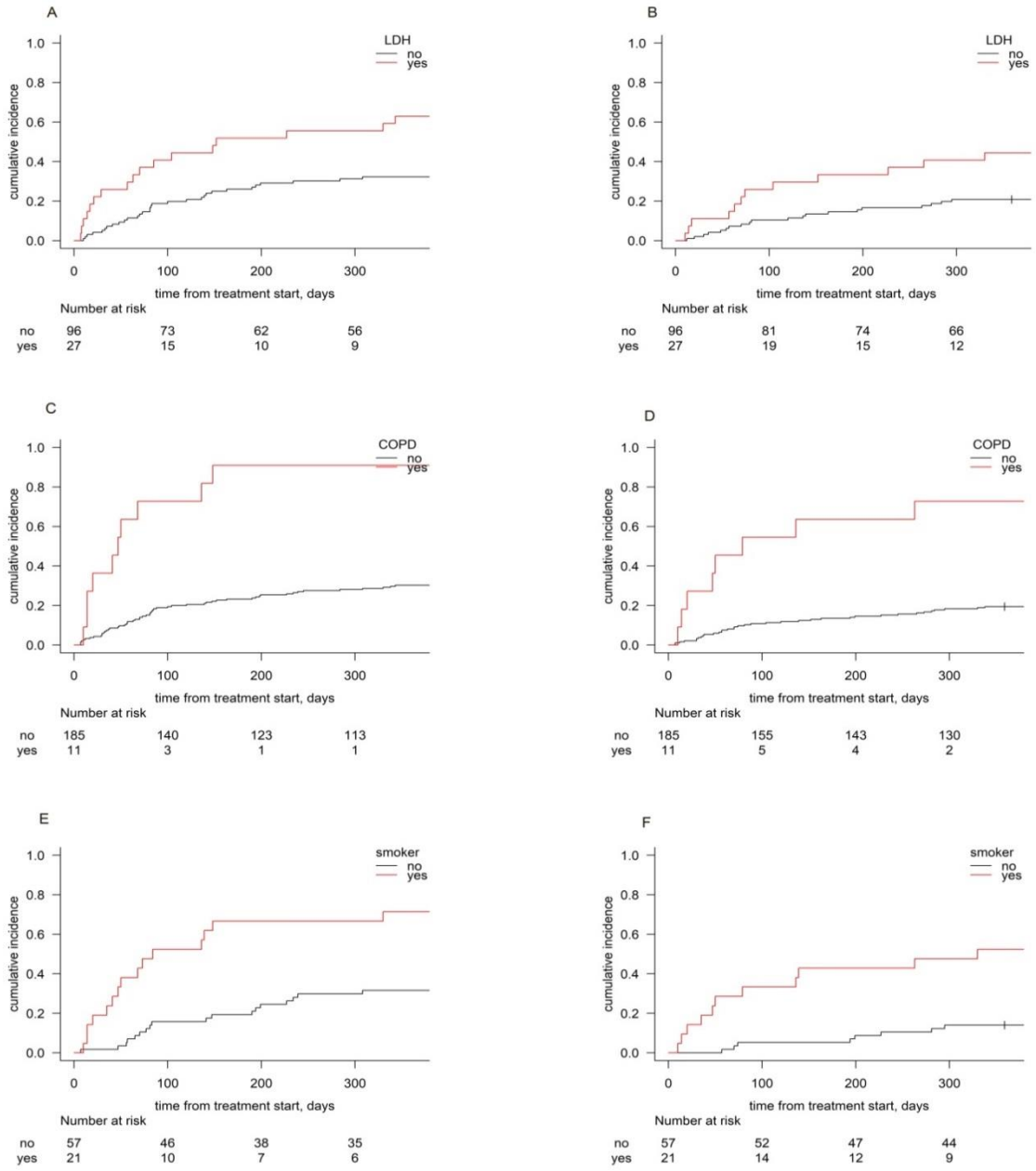


Figure (7): Cumulative incidence curses of infections: A) Cumulative incidence curves of all infections according to elevated LDH, B) Cumulative incidence curves of ≥G3 infections according to elevated LDH, C) Cumulative incidence curves of all infections according to COPD, D) Cumulative incidence curves of ≥G3 infections according to COPD, E) Cumulative incidence curves of all infections according to smoking, F) Cumulative incidence curves of ≥G3 infections according to smoking (KP8). This figure is obtained from Figure 1 of (Djebbari et al 2020, Haematologica), accessed from Haematologica Journal website (http://www.haematologica.org). Permission to re-use Figure 1 was obtained from Ferrata Storti Foundation.

5.2.4. Impact of my research, and future directions:

Managing infections associated with novel therapies has become a high priority for the myeloma community in recent years, as survival in this incurable cancer continues to improve. KP8 investigated the complexity of infections in elderly myeloma patients, and is the first study to assess the influence of an extensive number of patient, disease and treatment characteristics on infection occurrence, which can help clinicians in the early identification of high risk patients (KP8).

Cumulative incidence of all grade infections reported in KP8 (33%) is consistent with a combined analysis of 476 patients from two large NDMM trials (33.2%) (Offidani et al 2015). In contrast, the figure for ≥G3 infections (22%) was significantly higher than trial patients (11%), possibly as result of advanced age and co-morbidities in this real-world cohort of patients, most of whom would be trial-ineligible (KP8).

KP8 identified clinical predictors of infections and of infection-related hospitalisation. All these findings are helpful for clinicians to highlight at-risk groups (KP8).

Results described in KP8 are consistent with an analysis of the FIRST trial in TNE NDMM, where elevated LDH was retained in the definition of ≥G3 infections according to a validated prediction model (Dumontet et al 2018). KP8 results are also consistent with an Australian study of 199 patients which found no independent association between infections and the choice of therapy (IMiD vs. PI) (Teh et al 2015).

In light of all these data, we issued recommendations regarding baseline infection risk stratification of patients, using the predictors we identified.

TEAMM trial demonstrated that the prophylactic use of 12 weeks of levofloxacin 500mg daily for myeloma patients receiving therapy significantly reduced febrile episodes and deaths without increasing healthcare associated infections (Drayson et al 2019). Therefore, KP8 recommended instituting primary antibacterial prophylaxis for at-risk patients, or for those with a history of recurrent respiratory tract infections (KP8).

6. CONCLUDING REMARKS:

Myeloma remains an incurable cancer with a relapsing and a remitting course, but it has become increasingly more treatable (Ramasamy et al 2015). My journey in this field as a haematology pharmacist, independent prescriber in Oxford's myeloma clinic and as a researcher, has been quite challenging but very exciting because the therapeutic management of this condition witnessed a major revolution in the last decade particularly with the advent of novel agents from distinct pharmacological classes such as proteasome inhibitors (e.g. bortezomib, carfilzomib, ixazomib), newer immunomodulatory drugs (e.g. lenalidomide and pomalidomide) and CD38 monoclonal antibodies (daratumumab). Conducting real-world research in this area of therapeutics is absolutely paramount because clinical outcomes reported in clinical trials are not always replicated in routine care (Richardson et al 2018).

Real-world data in myeloma is a powerful platform which helps to understand outcomes in clinical practice. I embarked on a journey to address a number of questions which emerged from the increased usage of myeloma novel agents in routine care. My real-world research projects enabled a better understanding of how the use of a number of therapeutic agents and strategies can be optimised to improve clinical outcomes, particularly in elderly or frail patients or those with co-morbidities. In this introductory section, I selected eight key publications and demonstrated my contribution to the myeloma field with one key aim: optimising therapeutic outcomes whilst improving tolerability.

On the basis of the data demonstrated in the 6 retrospective studies and the large systematic review, a number of conclusions can be drawn. Bortezomib therapy remains a pillar in myeloma treatment. A cumulative bortezomib dose ≥50mg is associated with improved efficacy outcomes (OS and TTNT) (KP1). The use of triplets over doublet combinations can improve outcomes but this was not shown to be significant (KP1).

Carfilzomib therapy is efficacious and reasonably well tolerated despite old age and co-morbidities which characterise our real-world cohort (KP2). In the latter subgroup, a key strategy to maintain therapy and limit toxicity is to employ dose reductions early on during the course of treatment or upfront where necessary (KP2). In future, it would be important to investigate outcomes of a larger cohort to measure the extent of changes in practice based on our data, and if our results are replicated in other treatment centres.

The intensive cytotoxic chemotherapy DPACE still has a place in the era of myeloma novel therapies. However, KP3 demonstrated that this regimen can only be beneficial in extending TTNT if consolidated with an ASCT (KP3). On the other hand, it achieves a less than desirable outcome in non-ASCT-eligible patients, or those more heavily pre-treated (KP3).

The continuous therapy strategy in elderly TNE NDMM patients offered a significantly improved OS, PFS and TTNT, compared to FDT strategy where thalidomide is largely used (KP4). However, a future study can investigate the same comparison but where the FDT cohort is treated with bortezomib, a current standard of care in this is setting and a more novel agent than thalidomide.

TFI in elderly myeloma patients was shown to be longest after 1st line therapy (median=6.9 months) and declined with subsequent lines of therapy (KP5). This was also demonstrable across the different age and co-morbidity subgroups. In the future, we suggest to myeloma clinicians as well as research investigators to consider the TFI as an additional measure of efficacy in clinical practice, and as an exploratory endpoint in prospective clinical trials (KP5).

Evidence of non-standard dosing of oral anticancer agents in oncology and haematology was identified in 34 studies. The evidence for myeloma drugs was very limited (2 studies of moderate quality) (KP6, KP7).

Infections in elderly NDMM patients continue to pose a significant problem which is very complex to prevent or limit during the course of myeloma treatment (KP8). Baseline infection risk stratification needs to be employed by clinicians prior to starting therapy, using the clinical predictors identified in this study (KP8). In future, infection outcomes need to be re-evaluated to assess the role of the proposed risk stratification system. In addition, the prophylactic use of 12 weeks of levofloxacin 500mg daily for current myeloma patients receiving therapy (as per TEAMM trial) is strongly recommended (Drayson et al 2019). In view of the ongoing COVID-19 pandemic, it would also be important to assess infection outcomes in myeloma patients who contracted SARS-Cov-2, in addition to the impact of the recent changes to standard of care during the pandemic.

The methodologies described in this body of work had a number of advantages which helped me meet my objectives of answering some urgent research questions. Retrospective study design enables the assessment of a large myeloma cohort (e.g. n=272 in KP1, n=223 in KP4,

n=292 in KP5, and n=200 in KP8) conveniently using the electronic chemotherapy prescribing as well as patient records. As the lead investigator, I had the independence to explore all available patient/disease/treatment data in order to answer urgent or complex clinical questions which are encountered in clinical practice (e.g. conducting extensive data collection to enable UVA and MVA analyses to identify baseline characteristics associated with increased risk of myeloma infections, KP8).

The retrospective analysis of data about myeloma patients previously exposed to a given treatment choice or strategy represents an additional research platform to improve the understanding of these therapies in elderly patients with co-morbidities, who are largely under-represented in prospective phase 3 myeloma trials. This filled gaps in the literature.

My myeloma studies presented with a number of limitations which include their retrospective (less powerful than prospective studies), non-randomised nature, patient selection bias, under-reported toxicities and missing data. The small sample size was another limitation in the carfilzomib study (n=30) (KP2). In all of my real-world studies, I acknowledged all the limitations in the discussion sections of the published papers.

Specific limitations of each of the individual studies are as follows: KP1 (lack of AE data, lack of subgroup analyses according to cytogenetics, lack of frailty and co-morbidity data), KP2 (small sample size, and lack of KM survival curves for OS and PFS due to short follow up), KP3 (lack of complete AE data, lack of complete cytogenetics data, inability to conduct survival comparisons for OS and TTNT according to the choice DPACE, i.e. DTPACE vs. VTDPACE vs. VRDPACE), KP4 (a clinical trial cohort vs. a real-world cohort is not an ideal comparison, lack of co-morbidity, frailty, cytogenetic and AE data in the real-world cohort), KP5 (lack of AE data and cytogenetic data, lack of subgroup analysis according to R-ISS), KP6+KP7 (lack of reporting of full data from eligible papers in the systematic review, i.e. efficacy, AEs and QoL), and KP8 (risk of under-reporting/under-documentation of infective episodes in this retrospective dataset, and lack of complete cause of death data).

Real-world data continues to play an important role in improving clinical outcomes of myeloma patients. In view of the continuously changing myeloma treatment paradigm which will continue to recruit newer agents currently investigated or recently reported in clinical trials (e.g. isatuximab, selinexor, and belantamab), research questions originating from routine care will continue to be raised and will need to be addressed.

We need to continue to interrogate real-world myeloma data in the future in order to identify answers to pertinent therapeutic questions. I plan to address a number of research questions following the completion of my PhD. The safety and efficacy of the novel BCMA antibody-drug-conjugate belantamab need to be evaluated in the relapsed/refractory myeloma setting where this drug has recently been made available as part of a GSK compassionate use scheme. There is currently no real-world data describing myeloma outcomes with this novel class of therapeutics. In addition, isatuximab is a newer CD38 monoclonal antibody which demonstrated its efficacy and safety in combination with pomalidomide and dexamethasone (IsaPomDex) in the relapsed/refractory myeloma setting in a large phase 3 trial (Attal et al 2019). However, there is no data to describe outcomes in the real-world. I plan to investigate those outcomes nationally across the UK by recruiting all patients enrolled in the IsaPomDex compassionate use scheme offered by Sanofi.

In order to improve the quality of these 2 studies, I plan to modify some aspects of my methodology by: collaborating with investigators nationally (across the UK) instead of locally (Oxford) or regionally (Thames Valley) in order to maximise the sample size; performing data collection during the active management of the patient instead of after treatment completion (to reduce the risk of data misinterpretation and the amount of missing data); investigating adverse events in more depth; and conducting subgroup efficacy analyses (according to cytogenetics, age, and co-morbidities). Because myeloma is a disease of the elderly, I would like for all my future real-world studies to include a frailty and QoL assessment at baseline, during and at the end of therapy.

In summary to date, my research journey in the field of myeloma therapeutics has been full of challenges but it represented a significant learning curve, during which I developed my research skills and methods, and succeeded in leading a number of large cohort studies, and in collaborating with other myeloma researchers.

I achieved a good understanding of the conduct, methods and interpretation of real-world data. I have also demonstrated competence in conducting high quality literature research through my systematic review. I gained experience in leadership and management because I completed and published all my research studies I performed to date. Through my key publications, I answered a number of urgent clinical questions originating from clinical practice, and changed practice locally, regionally and nationally. I gained good experience in disseminating my research data in national, European and international haematology

conferences. I am also very experienced at of writing up my research findings and submitting to haematology journals, and responding to questions arising during the peer-review process. My experience to date with real-world research places me in a favourable position to continue to expand my myeloma research portfolio.

7. REFERENCES:

Acaster S, Gaugris S, Velikova G, Yong K & Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. Supportive Care in Cancer. 2013; 21(2):599-607

Anderson KC. Progress and Paradigms in Multiple Myeloma. Clin Cancer Res 2016; 22(22): 5419-5427.

Attal M, Richardson PG, Rajkumar SV, San-Miguel J, Beksac M, Spicka I, Leleu X, Schjesvold F, Moreau P, Dimopoulos MA, Huang JS, Minarik J, Cavo M, Prince HM, Macé S, Corzo KP, Campana F, Le-Guennec S, Dubin F, Anderson KC; ICARIA-MM study group. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019 Dec 7; 394(10214):2096-2107. doi: 10.1016/S0140-6736(19)32556-5. Epub 2019 Nov 14.

Augustson BM, Begum G, Dunn JA, Barth NJ, Davies F, Morgan G, Behrens J, Smith A, Child JA, Drayson MT. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002—Medical Research Council Adult Leukaemia Working Party. J Clin Oncology. 2005; 23(36):9219-926.

Barlogie B, Anaissie E, van Rhee F, Haessler J, Hollmig K, Pineda-Roman M, Cottler-Fox M, Mohiuddin A, Alsayed Y, Tricot G, Bolejack V, Zangari M, Epstein J, Petty N, Steward D, Jenkins B, Gurley J, Sullivan E, Crowley J, Shaughnessy JD Jr. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. Br J Haematol. 2007; 138(2):176-185.

Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, Pinto A, Weisel K, Ludwig H, Bahlis N, Banos A, Tiab M, Delforge M, Cavenagh J, Geraldes C, Lee JJ, Chen C, Oriol A, de la Rubia J, Qiu L, White DJ, Binder D, Anderson K, Fermand JP, Moreau P, Attal M, Knight R, Chen G, Van Oostendorp J, Jacques C, Ervin-Haynes A, Avet-Loiseau H, Hulin C, Facon T; FIRST Trial Team. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014; 371(10):906–917

Bianchi G, Anderson K. Understanding biology to tackle the disease: Multiple myeloma from bench to bedside, and back. CA Cancer J Clin. 2014; 64(6):422-444

Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, Ria R, Gentili S, Patriarca F, Nozzoli C, Levi A, Guglielmelli T, Benevolo G, Callea V, Rizzo V, Cangialosi C, Musto P, De Rosa L, Liberati AM, Grasso M, Falcone AP, Evangelista A, Cavo M, Gaidano G, Boccadoro M, Palumbo A. Efficacy and safety of once weekly bortezomib in multiple myeloma patients. Blood. 2010; 120(26):5250

Bringhen, S., Milan A, D'Agostino M, Ferri C, Wäsch R4, Gay F, Larocca A, Offidani M, Zweegman S, Terpos E, Goldschmidt H, Cavo M9, Ludwig H, Driessen C, Auner HW, Caers J, Gramatzki M, Dimopoulos MA, Boccadoro M, Einsele H, Sonneveld P, Engelhardt M. Prevention, monitoring and treatment of cardiovascular adverse events in myeloma patients receiving carfilzomib A consensus paper by the European Myeloma Network and the Italian Society of Arterial Hypertension. J Intern Med. 2019; 286(1):63-74

British Medical Association. British National Formulary. 73. London: BMJ group and Pharmaceutical Press; 2017. Royal Pharmaceutical Society.

Cancer Research UK. Myeloma Statistics (2013-2017). Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma (Accessed: 05 April 2020)

Chari A, Romanus K, Raju A, Farrelly E, Blazer M, Skacel T, Hari P. Duration of therapy (DOT) and time to next therapy (TTNT) of bortezomib, carfilzomib and ixazomib combinations with lenalidomide/dexamethasone (VRd, KRd, IRd) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): clinical practice in the United States vs clinical trial experience. Blood. 2017; 130 (Supplement 1): 1818

Chari A, Romanus K, Farrelly E, Huang H, Blazer M, Raju A, Noga S, Skacel T, Richardson P. Randomized clinical trial (RCT) representativeness and outcomes among relapsed/refractory multiple myeloma (RRMM) patients treated in the real world (RW): comparison of ASPIRE, TOURMALINE-MM1, POLLUX, AND ELOQUENT-2 RCTS. Clin. Lymphoma Myeloma Leuk. 2018; 18(Suppl. 1):S249

Chari A, Romanus D, Palumbo A, Blazer M, Farrelly E, Raju A, Huang H, Richardson P. Randomized Clinical Trial Representativeness and Outcomes in Real-World Patients: Comparison of 6 Hallmark Randomized Clinical Trials of Relapsed/Refractory Multiple Myeloma. Clin Lymphoma Myeloma Leuk 2020; 20(1): 8-17 e16.

Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, Lentzsch S, Munshi N, Palumbo A, Miguel JS, Sonneveld P, Cavo M, Usmani S, Durie BG, Avet-Loiseau H; International Myeloma Working Group. IMWG consensus on risk stratification in multiple myeloma. Leukemia. 2014; 28(2):269-77.

Costa LJ, Hari PN, Kumar SK. Differences between unselected patients and participants in multiple myeloma clinical trials in US: a threat to external validity. Leuk. Lymphoma. 2016; 57(12):2827–2832.

Dimopoulos M, Barlogie B, Smith TL, Alexanian R. High serum lactate dehydrogenase level as a marker for drug resistance and short survival in multiple myeloma. Ann Intern Med. 1991; 115:931–935.

Dimopoulos M, Kyle R, Fermand JP, Rajkumar SV, San Miguel J, Chanan-Khan A, Ludwig H, Joshua D, Mehta J, Gertz M, Avet-Loiseau H, Beksaç M, Anderson KC, Moreau P, Singhal S, Goldschmidt H, Boccadoro M, Kumar S, Giralt S, Munshi NC, Jagannath S; International Myeloma Workshop Consensus Panel 3. Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. Blood. 2011; 117(18):4701-4705.

Dimopoulos, M.A., Moreau P, Palumbo A, Joshua D, Pour L, Hájek R, Facon T, Ludwig H, Oriol A, Goldschmidt H, Rosiñol L, Straub J, Suvorov A, Araujo C, Rimashevskaya E, Pika T, Gaidano G, Weisel K, Goranova-Marinova V, Schwarer A, Minuk L, Masszi T, Karamanesht I, Offidani M, Hungria V, Spencer A, Orlowski RZ, Gillenwater HH, Mohamed N, Feng S, Chng WJ; ENDEAVOR Investigators. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016; 17(1):27-38

Djebbari F, Srinivasan A, Vallance G, Moore S, Kothari J, Ramasamy K (2018) Clinical outcomes of bortezomib-based therapy in myeloma. PLoS ONE. 2018: 13(12).

Djebbari F, Hubenov H, Neelakantan P, Wolf J, Offer M, Khera A, Louka E, Vallance G, Kothari J, Moore S, Ramasamy K. Carfilzomib therapy for relapsed myeloma: results of a UK multicentre experience. Br J Haematol. 2020; 188(4):57-60

Djebbari F, De Abrew K, Salhan B, Panitsas F, Hossain ME, Eyre TA, Willan J, Ramasamy K, Basu S, Jenner M, Kothari J.. DPACE-based chemotherapy in the era of myeloma novel agents: a UK multicentre study. Eur J Haematol. 2020. DOI:10.1111/ejh.13422

Djebbari F, Sharpley FA, McLain-Smith S, Vallance G, Eyre TA, Kothari J, Moore S, Ramasamy R. Treatment-free interval as an additional measure of efficacy in a large UK dataset of transplant ineligible myeloma patients. PLoS ONE. 2020 15(2)

Djebbari F, Stoner N, Lavender V. Non-conventional dosing of oral anticancer agents in oncology and malignant haematology: a systematic review protocol. Sys Rvs Journal. 2017; 6(1):244.

Djebbari F, Stoner N, Lavender V. A systematic review of non-standard dosing of oral anticancer therapies. BMC Cancer. 2018; 18(1):1154

Djebbari F, Panitsas F, Eyre TA, Prodger C, Davies F, Burton K, Khera A, Vallance G, Moore S, Kothari J, Peniket A, Ramasamy K. Infection-related morbidity in a large study of transplant non-eligible newly diagnosed myeloma patients treated with UK standard of care. Haematologica. Epub 2020 Jan 09. PMID: 31919073

Drayson MT, Bowcock S, Planche T, Iqbal G, Pratt G, Yong K, Wood J, Raynes K, Higgins H, Dawkins B, Meads D, Hulme CT, Monahan I, Karunanithi K, Dignum H, Belsham E, Neilson J, Harrison B, Lokare A, Campbell G, Hamblin M, Hawkey P, Whittaker AC, Low E, Dunn JA; TEAMM Trial Management Group and Trial Investigators. Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. Lancet Oncol. 2019; 20(12):1760-1772.

Dumontet C, Hulin C, Dimopoulos MA, Belch A, Dispenzieri A, Ludwig H, Rodon P, Van Droogenbroeck J, Qiu L, Cavo M, Van de Velde A, Lahuerta JJ, Allangba O, Lee JH, Boyle E, Perrot A, Moreau P, Manier S, Attal M, Roussel M, Mohty M, Mary JY, Civet A, Costa B, Tinel A, Gaston-Mathé Y, Facon T. A predictive model for risk of early

grade≥3 infection in patients with multiple myeloma not eligible for transplant: analysis of the FIRST trial. Leukemia. 2018; 32(6):1404-1413.

D'Agostino M, Bertamini L, Oliva S, Boccadoro M, Gay F. Pursuing a Curative Approach in Multiple Myeloma: A Review of New Therapeutic Strategies. Cancers (Basel) 2019; 11(12).

Electronic Medicines Compendium. Summary of Product Characteristics: Revlimid 25mg. Available from: http://www.medicines.org.uk/emc/medicine/29490 (Accessed 05 April 2017)

Facon T, Dimopoulos MA, Dispenzieri A, Catalano JV, Belch A, Cavo M, Pinto A, Weisel K, Ludwig H, Bahlis NJ, Banos A, Tiab M, Delforge M, Cavenagh JD, Geraldes C, Lee JJ, Chen C, Oriol A, De La Rubia J, White D, Binder D, Lu J, Anderson KC, Moreau P, Attal M, Perrot A, Arnulf B, Qiu L, Roussel M, Boyle E, Manier S, Mohty M, Avet-Loiseau H, Leleu X, Ervin-Haynes A, Chen G, Houck V, Benboubker L, Hulin C. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood. 2018; 131(3):301–310.

Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, Basu S, Nahi H, Hulin C, Quach H, Goldschmidt H, O'Dwyer M, Perrot A, Venner CP, Weisel K, Mace JR, Raje N, Attal M, Tiab M, Macro M, Frenzel L, Leleu X, Ahmadi T, Chiu C, Wang J, Van Rampelbergh R, Uhlar CM, Kobos R, Qi M, Usmani SZ; MAIA Trial Investigators. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. 2019; 380(22):2104-2115

Fields, P.A., Townsend, W., Webb, A., Counsell, N., Pocock, C., Smith, P., Jack, A., El-Mehidi, N., Johnson, P.W., Radford, J., Linch, D.C. & Cunnningham, D. (2014) De novo treatment of diffuse large B-cell lymphoma with rituximab, cyclophosphamide, vincristine, gemcitabine, and prednisolone in patients with cardiac comorbidity: a United Kingdom National Cancer Research Institute trial. J Clin Oncol. 2014; 32(4):282-287

Hulin C, Belch A, Shustik C, Petrucci MT, Dührsen U, Lu J, Song K, Rodon P, Pégourié B, Garderet L, Hunter H, Azais I, Eek R, Gisslinger H, Macro M, Dakhil S, Goncalves C, LeBlanc R, Romeril K, Royer B, Doyen C, Leleu X, Offner F, Leupin N, Houck V, Chen G, Ervin-Haynes A, Dimopoulos MA, Facon T. Updated Outcomes and Impact of Age With Lenalidomide and Low-Dose Dexamethasone or Melphalan, Prednisone, and

Thalidomide in the Randomized, Phase III FIRST Trial. J Clin Oncol. 2016; 34(30):3609-3617

International Myeloma Foundation (IMF). International Myeloma Working Group (IMWG) criteria for the diagnosis of multiple myeloma. 2014. Available at: https://www.myeloma.org/international-myeloma-working-group-imwg-criteria-diagnosis-multiple-myeloma (last accessed 24/05/2020)

Jackson GH, Davies FE, Pawlyn F, Cairns DA, Striha A, Collett C, Hockaday A, Jones JR, Kishore B, Garg M, Williams CD, Karunanithi K, Lindsay J, Jenner MW, Cook G, Russell NH, Kaiser MF, Drayson MT, Owen RG, Gregory WM, Morgan GJ, for the UK NCRI Haemato-oncology Clinical Studies Group. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2019; 20(1): 57–73.

Jagannath S, Roy A, Kish J, Lunacsek O, Globe D, Eaddy M, Kuriakose ET, Willey J, Butler-Bird S, Siegel D. Real-world treatment patterns and associated progression-free survival in relapsed/refractory multiple myeloma among US community oncology practices. Expert Rev Hematol 2016; 9(7): 707-717.

Johnsen AT, Tholstrup D, Petersen M. A., Pedersen L, Groenvold M. Health related quality of life in a nationally representative sample of haematological patients. Eur J Haematol 2009; 83(2): 139-148.

Katodritou E, Kyrtsonis MC, Delimpasi S, Kyriakou D, Symeonidis A, Spanoudakis E, Vasilopoulos G, Anagnostopoulos A, Kioumi A, Zikos P, Aktypi A, Briasoulis E, Megalakaki A , Repousis P, Adamopoulos I, Gogos D, Kotsopoulou M, Pappa V, Papadaki E, Fotiou D, Nikolaou E, Giannopoulou E, Hatzimichael E, Giannakoulas N, Douka V, Kokoviadou K, Timotheatou D, Terpos E. Real-world data on Len/Dex combination at second-line therapy of multiple myeloma: treatment at biochemical relapse is a significant prognostic factor for progression-free survival. Ann Hematol 2018; 97(9): 1671-1682.

Klausen TW, Gregersen H, Abildgaard N, Andersen NF, Frølund UC, Gimsing P, Helleberg C, Vangsted AJ . The majority of newly diagnosed myeloma patients do not fulfill the inclusion criteria in clinical phase III trials. Leukemia 2019; 33(2): 546-549

Knauf W, Aldaoud A, Hutzschenreuter U, Klausmann M, Dille S, Wetzel N, Jänicke M, Marschner N, and the TLN-Group (Tumour Registry Lymphatic Neoplasms). Survival of non-transplant patients with multiple myeloma in routine care differs from that in clinical trials-data from the prospective German Tumour Registry Lymphatic Neoplasms. Ann Hematol 2018; 97(12): 2437-2445.

Kyle RA, Rajkumar SV. Multiple Myeloma. Blood. 2008; 111(6): 2962–2972.

Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009; 23 (1):3-9.

Lakshman A, Singh PP, Rajkumar SV, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Dingli D, Hwa YL, Fonder AL, Hobbs M, Hayman SR, Zeldenrust SR, Lust JA, Russell SJ, Leung N, Kapoor P, Go RS, Lin Y, Gonsalves WI, Kourelis T, Warsame R, Kyle RA, Kumar SK. Efficacy of VDT PACE-like regimens in treatment of relapsed/refractory multiple myeloma. Am J Hematol. 2018; 93(2):179-186.

Lee C-K, Barlogie B, Munshi N, Zangari M, Fassas A, Jacobson J, van Rhee F, Cottler-Fox M, Muwalla F, Tricot G. DTPACE: an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. J Clin Oncol. 2003; 21(14):2732-2739.

Lopez A, Mateos MV, Oriol A, Valero M, Martínez J, Lorenzo JI, Perez M, Martinez R, de Paz R, Granell M, De Arriba F, Blanchard MJ , Peñalver FJ, Bello JL, Martin ML, Bargay J, Blade J, Lahuerta JJ, San Miguel JF , de la Rubia J. Patterns of relapse and outcome of elderly multiple myeloma patients treated as front-line therapy with novel agents combinations. Leuk Res Rep 2015; 4(2): 64-69.

Mangiacavalli S, Albani G, Caravita T, Cocito F, Pascutto C, Zappasodi P, Bringhen S, Palumbo A, Cazzola M, Corso A. Similar neurotoxicity of an alternating compared to a continuous low-dose schedule of thalidomide for relapsed/refractory multiple myeloma. Leuk Lymphoma. 2012; 53(3):514–515.

Mangiacavalli S, Cocito F, Ferretti VV, Ganzetti M, Salvatore Cartia C and Corso A. The advantages of switch to subcutaneous bortezomib in the real life. Leuk Lymphoma. 2018; 59(6):1505-1507

Mateos MV, Richardson PG, Dimopoulos MA, Palumbo A, Anderson KC, Shi H, Elliott J, Dow E, van de Velde H, Niculescu L, San Miguel JF. Effect of cumulative bortezomib dose on survival in multiple myeloma patients receiving bortezomib-melphalan-prednisone in the phase III VISTA study. Am J Hematol. 2015; 90(4):314-319

Mateos M.V & San Miguel J.F. Management of multiple myeloma in the newly diagnosed patient. Hematology Am Soc Hematol Educ Program. 2017; 2017(1):498-507

Mateos M.V., Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, Doyen C, Lucio P, Nagy Z, Kaplan P, Pour L, Cook M, Grosicki S, Crepaldi A, Liberati AM, Campbell P, Shelekhova T, Yoon SS, Iosava G, Fujisaki T, Garg M, Chiu C, Wang J, Carson R, Crist W, Deraedt W, Nguyen H, Qi M, San-Miguel J; ALCYONE Trial Investigators. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med. 2018; 378(6):518-528

Matsue K, Matsue Y, Fujisawa M, Fukumoto K, Suehara Y, Sugihara H, Takeuchi M. Clinical features and treatment outcome of very elderly patients over 80 years old with multiple myeloma: comparison with patients in different age groups in the era of novel agents. Leuk Lymphoma. 2016; 57(1):110-115

Minarik J, Pavlicek P, Pour L, Pika T, Maisnar V, Spicka I, Jarkovsky J, Krejci M, Bacovsky J, Radocha J, Straub J, Kessler P, Wrobel M, Walterova L, Sykora M, Obernauerova J, Brozova L, Gregora E, Adamova D, Gumulec J, Adam Z, Scudla V, Hajek R; Czech Myeloma Group. Subcutaneous Bortezomib in Multiple Myeloma Patients Induces Similar Therapeutic Response Rates as Intravenous Application But It Does Not Reduce the Incidence of Peripheral Neuropathy. PLoS One. 2015; 10(4)

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015; 4 (1).

Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, Rekhtman G, Masliak Z, Robak T, Shubina A, Arnulf B, Kropff M, Cavet J, Esseltine DL, Feng H, Girgis S, van de Velde H, Deraedt W, Harousseau JL. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol. 2011; 12(5):431–40.

Moreau P, Mateos MV, Berenson JR, Weisel K, Lazzaro A, Song K, Dimopoulos MA, Huang M, Zahlten-Kumeli A, Stewart AK. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study. Lancet Oncol. 2018; 19(7):953-964

National Institute for Care and Clinical Excellence. 2007. Bortezomib monotherapy for relapsed multiple myeloma. Available from: https://www.nice.org.uk/guidance/ta129 (Accessed 05 April 2020)

National Institute for Care and Clinical Excellence. 2011. Bortezomib and thalidomide for the first‑line treatment of multiple myeloma. Available from: https://www.nice.org.uk/Guidance/ta228 (Accessed 05 April 2020)

National Institute for Care and Clinical Excellence. 2014. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. Available from: https://www.nice.org.uk/guidance/ta311 (Accessed 05 April 2020

National Institute for Health and Care Excellence. 2017. Carfilzomib for previously treated multiple myeloma. Available from: https://www.nice.org.uk/guidance/ta457 (Accessed 05 April 2020).

National Institute for Health and Care Excellence. 2019. Lenalidomide plus dexamethasone for previously untreated multiple myeloma. Available from: https://www.nice.org.uk/guidance/TA587 (Accessed 05 April 2020).

Niesvizky R, Flinn IW, Rifkin R, Gabrail N, Charu V, Clowney B, Essell J, Gaffar Y, Warr T, Neuwirth R, Zhu Y, Elliott J, Esseltine DL, Niculescu L, Reeves J. Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens. J Clin Oncol. 2015; 33(33):3921-3929

Offidani M, Corvatta L, Bringhen L, Gentili S, Gay F, Maracci L, Boccadoro M, Leoni P, Palumbo A. Infection Complications in 476 Patients with Newly Diagnosed Multiple Myeloma Treated with Lenalidomide or Bortezomib Combinations. Blood. 2015; 126(23):5365.

Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011; 364(11):1046-1060.

Palumbo A., Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, Gisslinger H, Wiktor-Jędrzejczak W, Zodelava M, Weisel K, Cascavilla N, Iosava G, Cavo M, Kloczko J, Bladé J, Beksac M, Spicka I, Plesner T, Radke J, Langer C, Ben Yehuda D, Corso A, Herbein L, Yu Z, Mei J, Jacques C, Dimopoulos MA; MM-015 Investigators. MM-015 Investigators. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med. 2012; 366(19):1759-1769

Palumbo A, Bringhen S, Larocca A, Rossi D, Di Raimondo F, Magarotto V, Patriarca F, Levi A, Benevolo G, Vincelli ID, Grasso M, Franceschini L, Gottardi D, Zambello R, Montefusco V, Falcone AP, Omedé P, Marasca R, Morabito F, Mina R, Guglielmelli T, Nozzoli C, Passera R, Gaidano G, Offidani M, Ria R, Petrucci MT, Musto P, Boccadoro M, Cavo M. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival. J Clin Oncol. 2014; 32(7):634-40.

Palumbo A, Avet-Loiseau H, Oliva S , Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, Bringhen S, Gay F, Attal M, Passera R, Spencer A, Offidani M, Kumar S, Musto P, Lonial S, Petrucci MT, Orlowski RZ, Zamagni E, Morgan G, Dimopoulos MA, Durie BGM, Anderson KC, Sonneveld P, San Miguel J, Cavo M, Rajkumar SV, Moreau P. Revised International Staging System for Multiple Myeloma: A Report from International Myeloma Working Group. J Clin Oncol. 2015; 10;33(26):2863-9.

Popat R, Khan I, Dickson J, Cheesman S, Smith D, D'Sa S, Rabin N, Yong K. An alternative dosing strategy of lenalidomide for patients with relapsed multiple myeloma. Br J Haematol. 2015; 168(1):139–159.

Pulte ED, Nie L, Gormley N, Goldberg KB, McKee A, Farrell A, Pazdur R. Survival of ethnic and racial minority patients with multiple myeloma treated with newer medications. Blood Adv. 2018; 2(2):116–119.

Ramasamy K, Lonial S. Fast Facts: Multiple Myeloma and Plasma Cell Dyscrasias. 1st ed. Oxford: Health Press Ltd; 2015.

Richardson PG, San Miguel JF, Moreau P, Hajek R, Dimopoulos MA, Laubach JP, Palumbo A, Luptakova K, Romanus D, Skacel T, Kumar SK, Anderson KC. Interpreting clinical

trial data in multiple myeloma: translating findings to the real-world setting. Blood Cancer J. 2018; 8(11):109.

San Miguel J.F., Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, Spicka I, Petrucci MT, Palumbo A, Samoilova OS, Dmoszynska A, Abdulkadyrov KM, Schots R, Jiang B, Mateos MV, Anderson KC, Esseltine DL, Liu K, Cakana A, van de Velde H, Richardson PG; VISTA Trial Investigators. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008; 359(9):906-917

Shah JJ, Abonour R, Gasparetto C, Hardin JW, Toomey K, Narang M, Srinivasan S, Kitali A, Zafar F, Flick ED, Rifkin RM. Analysis of common eligibility criteria of randomized controlled trials in newly diagnosed multiple myeloma patients and extrapolating outcomes. Clin. Lymphoma Myeloma Leuk. 2017; 17(9):572–583

Sharpley FA, Djebbari F, Fourali S, Kothari J, Lynes JA, McLain-Smith S, Ramasamy K. Clinical outcomes with fixed-duration therapy (UK real-world data) compared with continuous lenalidomide and low-dose dexamethasone therapy (FIRST trial; MM-020) for transplant-ineligible patients with newly-diagnosed multiple myeloma. Leuk Lymphoma. 2020; 61(3):732-736

Teh BW, Harrison SJ, Pellegrini M, Thursky KA, Worth LJ, Slavin, M.A. Changing treatment paradigms for patients with plasma cell myeloma: impact upon immune determinants of infection. Blood Rev. 2014; 28(2):75-86.

Teh BW, Harrison SJ, Worth LJ, Spelman T, Thursky KA, Slavin MA. Risks, severity and timing of infections in patients with multiple myeloma: a longitudinal cohort study in the era of immunomodulatory drug therapy. Br J Haematol. 2015; 171(1):100-108.

Wilke T, Mueller S, Bauer S, Pitura S, Probst L, Ratsch BA, Salwender H. Treatment of relapsed refractory multiple myeloma: which new PI-based combination treatments do patients prefer? Patient Prefer Adherence 2018; 12: 2387-2396.

World Cancer Research Fund International. Worldwide Cancer Data. Available from: http://www.wcrf.org/int/cancer-facts-figures/worldwide-data (Accessed 05 April 2020)

Yuen HLA, Low MSY, Fedele P, Kalff A, Walker P, Bergin K, Coutsouvelis J, Grigoriadis G, Spencer A. DCEP as a bridge to ongoing therapies for advanced relapsed and/or refractory multiple myeloma. Leuk Lymphoma. 2018; 59(12):2842-2846.

Yong K., Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, Safaei R, Karlin L, Mateos MV, Raab MS, Schoen P, Cavo M. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol. 2016; 175(2):252-264

Zweegman S, Engelhardt M, Larocca A; EHA SWG on 'Aging and Hematology'. Elderly patients with multiple myeloma: towards a frailty approach?. Curr Opin Oncol. 2017;29(5):315-321.

8. APPENDIX 1: OTHER PUBLICATIONS NOT INCLUDED IN THIS THESIS

In addition to the key publications (KP) used in this introductory section, I have contributed to a number of other published papers (listed below) in prestigious peer-reviewed journals, both in myeloma and lymphoma, either as Lead author or significantly contributing author. I refer to them as other publications (OP) 1-12. I have also described briefly 3 of the most influential lymphoma papers:

- **OP1:Djebbari F,** Browning JA, Stanton L, Booth S, Hildyard C, Willan J, Bosworth J, Vora SM, Hatton CSR, Collins GP, Eyre TA. Efficacy of R-GCVP in patients with late relapse of diffuse large B-cell lymphoma. Br J Haematol. 2019;186(6):191-195.

  I led this TVCN-wide UK multicentre study to investigate the efficacy and safety of R-GCVP (rituximab with gemcitabine, cyclophosphamide, vincristine and prednisolone) in patients with diffuse large B-cell lymphoma (DLBCL) presenting with late relapse (Djebbari et al 2019). This treatment is often only used as first line in patients with cardiac co-morbidities who cannot receive anthracyclines (doxorubicin) as part of R-CHOP (rituximab with doxorubicin, cyclophosphamide, vincristine and prednisolone) (Fields et al 2014). The rationale for the study is the absence of data on what is the best treatment for late relapse in patients who previously received R-CHOP as first line therapy and cannot receive it again at relapse. I focused on response rates, OS and PFS, in addition to toxicity outcomes. My study demonstrated that R-GCVP was a reasonably well tolerated treatment strategy with proven efficacy in an elderly cohort of patients with late DLBCL relapse. The AE profile of this therapy was similar to what was observed in the original R-GCVP trial (Fields et al 2014) (OP1).

  My R-GCVP study was the first to describe outcomes of this therapy for patients with DLBCL presenting with late relapse. Response rates were quite high. However, I did not find differential responses or survival according to prior rituximab exposure or length of first remission. This finding requires further evaluation in large prospective studies. This study is useful for lymphoma clinicians across the world, if they encounter a scenario of late DLBCL relapse (previously treated with R-CHOP) with the new knowledge from my study, showing that R-GCVP is a clinically robust option for this indication.

  I contributed towards the study methodology (data parameters to be collected). I contributed to data collection and co-ordinated the study with other UK participating centres. I performed data analysis in Tables (baseline characteristics and toxicity tables). I led on writing the manuscript. I estimate my total contribution at 40-50%.

- **OP2:** Eyre TA, **Djebbari F**, Kirkwood AA, Collins GP. A systematic review of the efficacy of CNS prophylaxis with stand-alone intrathecal chemotherapy in diffuse large B cell lymphoma patients treated with anthracycline-based chemotherapy in the rituximab era. Haematologica. Epub: 2019 Sep 5.PMID: 31488560

I made a significant contribution to this game-changing lymphoma systematic review on the efficacy of central nervous system (CNS) prophylaxis with stand-alone intrathecal (IT) chemotherapy in DLBCL patients treated with anthracycline-based chemotherapy in the rituximab era (Eyre et al 2019A). In recognition of my previous success at conducting a large systematic review, the lymphoma research team nominated me to lead on the search strategy for this review, in order obtains a timely answer to this urgent clinical question.

CNS relapse of DLBCL remains uncommon but a very poor outcome. The efficacy of stand-alone IT prophylaxis in preventing/reducing CNS relapse remains unclear. No systematic review has attempted to answer this question in the era of anti-CD20 monoclonal antibody (mab) therapy. I conducted a systematic and comprehensive search (2002-2019) using Ovid MEDLINE®, Ovid EMBASE® and Cochrane Central Register of Controlled Trials. Out of a total of 804 results screened using a careful inclusion and exclusion criteria, 14 studies were eligible for inclusion: 3 post hoc analyses, 1 prospective and 10 retrospective series (Eyre et al 2019A).

I found no evidence of benefit for IT prophylaxis in preventing CNS relapse in DLBCL in the rituximab era (Eyre et al 2019A). My systematic review was highly valued by expert reviewers in the journal Haematologica, and by the lymphoma community after publication of the paper. This led to a change in practice in TVCN and other parts of the UK, by limiting the use of IT MTX in DLBCL only to carefully selected patients.

I contributed towards the conception and design of this systematic review. I conducted the full search strategy and obtained the results. I contributed towards the inclusion/exclusion of studies, but not to quality appraisal. I contributed to the manuscript by writing the methods section, and by leading on submission to Haematologica. I estimate my total contribution to this project to be 40-50%.

- **OP3**: Eyre TA, Martinez-Calle N, Hildyard C, Eyre DW, Plaschkes H, Griffith J, Wolf J, Fields P, Gunawan A, Oliver R, **Djebbari F**, Booth S, McMillan A, Fox CP, Bishton MJ, Collins GP, Hatton CSR. Impact of intended and relative dose intensity of R-CHOP in a large, consecutive cohort of elderly diffuse large B-cell lymphoma patients treated with curative intent: no difference in cumulative incidence of relapse comparing patients by age. J Intern Med. 2019; 285(6):681-692.

I was a collaborator on this very large (n=790) UK-wide study of dose intensity of R-CHOP in elderly patients treated for DLBCL. The rationale for the study is that co-morbidities and frailty in older patients often contribute to treatment-related toxicities, which place a burden on the healthcare setting. Better dosing strategies are required to treat older patients whilst maintaining tolerability (Eyre et al 2019B)

This study examined the influence of intended and relative dose intensities (IDI and RDI) of the doxorubicin and cyclophosphamide components of R-CHOP, in addition to influence of age and co-morbidities, on clinical outcomes (Eyre et al 2019B).

The study demonstrated that PFS and OS were significantly inferior in patients ≥80 vs. 70–79 years (P < 0.001). In patients aged 70–79 years, PFS and OS were longer (P < 0.001) with IDI ≥80% compared to IDI < 80%. However, in patients ≥80 years, there was no difference in PFS (P = 0.88) or OS (P = 0.75) according to IDI. MVA showed that cumulative incidence of relapse in patients aged 70-79 was higher if IDI <80% was used (P=0.04), but using different IDIs in the older subgroup showed no difference (P=0.32) (Eyre et al 2019B).

This was the largest real-world clinical study I have been involved in (n=790). It reported very strong data arguing in favor of the use of attenuated R-CHOP dosing (i.e. R-mini-CHOP) to provide sufficient efficacy, and should be considered as a reasonable alternative approach to treat patients ≥80 years, with curative intent (Eyre et al 2019B). Practice across the UK started to implement this approach in treating older patients (R-mini-CHOP is the new standard of care in patients ≥ 80 years).

I contributed towards data collection: dose intensity of doxorubicin and cyclophosphamide for Oxford patients, the choice of CNS prophylaxis (intrathecal or IV) in addition to preparing dose intensity of vincristine in case requested by reviewers. I contributed towards the review of the manuscript. I led on the submission of the written manuscript to the Journal of Internal Medicine on behalf of the first other. I estimate my total contribution to be at least 5%.

- **OP4:** **Djebbari F**, Tatarczuch M, Panitsas F, Vallance G, Sultanova M, Kothari J, Ramasamy K, Peniket A. Resource implications of bortezomib therapy in a large UK cohort: An evaluation study. J Oncol Pharm Pract. 2019; 25(8):1995-1998

  This work was originally led by Dr Tatarczuch but I took the lead role after he moved back to Australia. I contributed towards data and to the interpretation of findings. I led on writing the manuscript, submission and publication of the paper, and I prepared the full responses to questions raised by peer reviewers. I estimate my total contribution at 30%

- **OP5:** Khera A, Panitsas F, **Djebbari F**, Kimberger K, Stern S, Quinn J, Rabin N, Kothari J, Alchi B, Haynes R, Winearls C, Roberts I, Ramasamy K. Long term outcomes in monoclonal gammopathy of renal significance. Br J Haematol. 2019; 186(5):706-716.

  I contributed towards data collection, contextualisation and prioritisation of findings. I supported the first author in writing the manuscript. I estimate my total contribution at 15%

- **OP6:** Panitsas F, Kothari J, Vallance G, **Djebbari F**, Ferguson L, Sultanova M, Ramasamy K. Treat or palliate: Outcomes of very elderly myeloma patients. Haematologica. 2018; 103(1):32-34

  I contributed towards review, discussion and feedback about the findings. I contributed towards review and editing of the manuscript. I estimate my total contribution at 5-10 %

- **OP7:** Willan J, King AJ, **Djebbari F**, Turner GDH, Royston DJ, Pavord S, Collins GP, Peniket A. Assessing the Impact of Lockdown: Fresh Challenges for the Care of

Haematology Patients in the COVID-19 Pandemic. Br J Haematol. 2020 May 5. doi: 10.1111/bjh.16782. [Epub ahead of print]

I contributed with data collection of chemotherapy patients, those receiving IV rituximab, SC bortezomib, and zoledronic acid, in addition to data about autologous transplants and allogeneic transplants. I estimate my total contribution to this project to be 25-30%.

- **OP8: Djebbari F**, Ramasamy K. Insights into daratumumab. Myeloid and Lymphoid Disorders in Practice. 2016; 1(1).

  For this review article published in the Myeloid and Lymphoid Disorders in Practice, I designed the article and its contents. I have fully written the paper, which was approved by the senior author. I estimate my total contribution at 80%.

- **OP9: Djebbari F**, Schuh A. Venetoclax for 17p deletion chronic lymphocytic leukaemia. Myeloid and Lymphoid Disorders in Practice. 2017; 2(2).

  For this review article published in the Myeloid and Lymphoid Disorders in Practice, I designed the article and its contents. I have fully written the paper, which was approved by the senior author. I estimate my total contribution at 80%.

- **OP10: Djebbari F**, Spiers L, Mole D, Protheroe A, Tuthill M. Renal cell carcinoma: novel medical therapies and management of renal toxicities. British Journal of Renal Medicine. 2019; 29 (2)

  For this review article and management guidance published in the British Journal of Renal Medicine, I designed the article and its contents, with support from Dr Tuthill my senior author. I have contributed to literature review. I led on writing the manuscript, and publication of the paper.

- **OP11: Djebbari F**, Panitsas F, Sharpley FA, Rampotas A, Larham J, Moore S, Gooding S, Kothari J, Ramasamy K. Myeloma care adaptations in the UK during SARS-CoV-2 pandemic: Challenges and measurable outcomes. Eur J Haematol. 2020 Jun 26;10.1111/ejh.13479. doi: 10.1111/ejh.13479. Online ahead of print.

  I conceived this article. I have performed the majority of literature searching and have written the paper. I estimate my contribution at 80%

- **OP12: Djebbari F**, Kaji F, Stanton L, Lawrence MM, Collins GP, Eyre TA. Efficacy and infection morbidity of front-line immuno-chemotherapy in follicular lymphoma. Eur J Haematol. 2020 Jul 15. doi: 10.1111/ejh.13486. Online ahead of print.

  I designed the study along with my senior author. I collected data, supported the analysis and I have written the paper. I estimate my contribution at least 50%

9. APPENDIX 2: TESTIMONIALS FROM CLINICIANS ABOUT THE AUTHOR'S PRACTICE-CHANGING RESEARCH:

Statement from Dr Andy Peniket, Haematology Consultant in Myeloma at Oxford University Hospitals NHS Foundation Trust, and Lead Clinician for Bone Marrow Transplant (BMT) at Thames Valley Cancer Network (TVCN)

Statement from Dr Graham P. Collins, Haematology Consultant at Oxford University Hospitals NHS Foundation Trust, and Lead Clinician for Lymphoma at Thames Valley Cancer Network (TVCN)

10. APPENDIX 3: STATEMENTS FROM SENIOR AUTHORS (SUPERVISORS) TO CONFIRM AUTHOR CONTRIBUTION:

Statement from Dr Karthik Ramasamy, Haematology Consultant in Myeloma at Oxford University Hospitals NHS Foundation Trust, and Lead Clinician for Myeloma at Thames Valley Cancer Network (TVCN). Dr Ramasamy is the senior author and supervisor of all the myeloma real-world studies included in this thesis.

Statement from Dr Verna Lavender, Head of Guy's Cancer Academy, and Honorary Senior Clinical Lecturer, School of Cancer & Pharmaceutical Sciences, KCL. Also, President of UK Oncology Nursing Society. Dr Lavender is the senior author of the 2 systematic review papers: the protocol and the findings.

Statement from Prof Ana Schuh, Director of Molecular Diagnosis at the University of Oxford, Haematology Consultant in CLL at Oxford University Hospitals NHS Foundation Trust, and Lead Clinician for CLL at Thames Valley Cancer Network (TVCN)

Statement from Dr Mark Tuthill, Consultant in Uro-Oncology at Oxford University Hospitals NHS Foundation Trust