Evolution or revolution in multiple myeloma therapy and the role of the UK

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Summary

The knowledge of disease biology as well as the therapeutic landscape in multiple myeloma (MM) has expanded exponentially in recent years. These advances have seen improvements in survivorship, not only in the clinical trial setting but also in the real setting. Importantly there is also every evidence to indicate that such improvements in our understanding and treatments will continue. This article is not intended to be a comprehensive review; rather it aims to give a temporal context to these developments with exemplars, and highlight the central role that UK clinicians, healthcare workers, scientists and most importantly patients and their relatives have played in this revolution.

Keywords: evolution, revolution, multiple myeloma therapy.

I (CM) started working in Belfast in 1968 under Prof. M. G. Nelson at a time when melphalan had been recently introduced for multiple myeloma (MM), and completed my MD thesis in 1975 under the guidance of Drs Tom McNeill and John Bridges. Returning to the Belfast City Hospital in 1978 after a two-year fellowship in Sydney Hospital working with Prof. Fred Gunz and the inspirational Dr Paul Vincent, I joined forces with Dr Jeffrey Robertson, developing autologous transplantation in Northern Ireland. I was instrumental in developing the UK Myeloma Forum, a society for UK clinicians, healthcare workers and scientists, (UKMF: www.ukmf.org.uk), which led the way in popularising disease-focused meetings for haematologists. I chaired the EBMT Chronic Malignancy Working Party Plasma Cell Disorders subcommittee and since 'retirement' I have continued some clinical work on a part-time basis, mainly at Altnagelvin Hospital.

I (GC) was introduced to MM through Prof. Ian Franklin in 1992, who mentored me through my PhD and higher specialist training. I then moved to Leeds in 2002 to work with Prof. Tony Child, Prof. Gareth Morgan and Prof. Julia Brown in clinical trials. At the time of becoming interested in MM, clinical care and trial innovation were sedentary though were about to undergo an exponential change both in treatment options and clinical trials (see below). Though the United Kingdom had a prominent heritage in myeloma clinical trials, as such we were not an established trials collaborative, able to compete internationally especially in the era of novel agents. I set up the Myeloma Research Alliance (UKMRA; www.ukmf.org.uk/clinical-trials-2/uk-mra/) in 2014, which has grown year-on-year in its impact, engendering engagement, especially with young researchers to harness the quality of clinical academics in the United Kingdom.

Development of the field

Therapeutics

Following the first description of MM,[1] therapeutic interventions which ranged from rhubarb and orange peel infusions to therapeutic venesection, quinine, camphor, Dover's powders and urethane, were of limited value.[2] Melphalan had been introduced for MM in the early 1960s but for haematologists, MM was still considered the 'heart sink' disease as responses were limited with treatment toxicities (cytopenias) and disease-related morbidity being significant issues. Treatment certainly had limited impact on the progression of myeloma-related end organ toxicity such as bone disease and chronic renal impairment.[3] In the early MRC Adult Leukaemia Working Party Myeloma trials alternative alkylating agents (with or without prednisone) were trialled against or in combination with melphalan but with no real improvement on the 24–30 months median survival of that era.[4] However, the MRC Myeloma V trial led to the ABCM combination [adriamycin, BCNU (bis-chloroethylnitrosourea), cyclophosphamide and melphalan] becoming briefly the UK 'gold standard' though the use of oral weekly cyclophosphamide (C-weekly) performed surprisingly well, especially in patients with cytopenias.[5] A summary of the MRC/NCRI trials and their major findings is presented in Table I.

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Table I. Summary baseline characteristics for the MRC/NCRI trials.

Trial	Years	*n*	Age	Sex % male	Allocation	*n* (randomised)	Outcome
I*	1964–1968	276	–		Cont. Cyclo PO		No significant difference
					Cont. Mel PO		
II*	1968–1975	372	–		Cont. Cyclo PO		No significant difference
					7-day PO Mel (M7) Q6-8/52		
					7-day PO Mel Q6-8/52 + Pred		
III*	1975–1980	485	<75		Iv Cyclo Q3/52		No significant difference
					M7 + Pred Q3/52		
					Iv Cyclo Q3/52		
					Cy/Mel/CCNU/Pred Q4/52		
IV*	1980–1982	522	<80		M7 + P		No significant difference
					M7 + PV		Hydration very important
V*	1982–1986	691	62·1 (8·4)	55·1	C-wkly plts < 80	61	ABCM superior
					M7	316	C-wkly useful with low toxicity
					ABCM	314	
VI*	1986–1991	712	61·6 (8·1)	57·9	ABCM	342	No significant difference
	1991–1993	299			ABCM-P	342	
					HDM (M140)	15	
					HDMP	13	
					NR ABCM	299	
VII* (TE)	1993–2000	401	54·8 (4·8)	55·6	ABCM	200	HDM + ASCT superior
					HDM + ASCT	201	
VIII* (TNE)	1993–2002	592	67·5 (4·8)	58·1	ABCM	167	No significant difference
					ABCM + C-wkly	164	
					NR	261	
IX* (TE)	2003–2007	1111	57·8 (7·4)	62·3	Clo + CVAD	278	CTD superior
					Clo + CTD	278	Zol superior
					Zol + CVAD	278	
					Zol_CTD	277	
IX*	2003–2007	849	73·4 (5·5)	55·7	Clo + MP	211	CTDa superior
(TNE)					Clo + CTDa	212	Zol superior
					Zol + MP	212	
					Zol + CTDa	214	
X† (REL)	2008–2012	297	60	70	PAD + HDM/2nd ASCT	89	PAD effective in 1st relapse
					PAD + Intensive C-wkly	85	ASCT superior
XI† (TE)	2010–2014	1512	59·1 (8·1)	59·2	CTD	756	CRD improves PFS and OS
					CRD	756	Addition of CVD improves PFS and OS
					CVD for poor responders		R maintenance improves PFS and OS
					R and RZ maintenance		
XI† (TNE)	2010–2015	1852	74·5 (5·4)	56·5	CTDa	924	R maintenance improves PFS
					RCDa	928	
					CVD for poor responders		
					R and RZ maintenance		
XI+† (TE)	2013–2016	1056	59·8 (8·0)	60·9	CTD	265	KRCD improves PFS
					CRD	265	
					KCRD	526	
					R maintenance		

MP, melphalan, prednisolone; C-wkly plts, cyclophosphamide-weekly for low platelets; M7, melphalan; ABCM, doxorubicin, carmustine, cyclophosphamide and melphalan; HDM, high-dose melphalan; HDM + ASCT, high-dose melphalan and autologous stem cell support; Clo, clodronic acid; Zol, zoledronic acid; CTD, cyclophosphamide, thalidomide and dexamethasone; CVAD, cyclophosphamide, vincristine, doxorubicin and dexamethasone; PAD, bortezomib (PS-341) adriamycin and dexamethasone; CTDa, attenuated oral CTD; CRD, cyclophosphamide, lenalidomide and dexamethasone; CRDa, attenuated oral CRD; CVD cyclophosphamide, bortezomib and dexamethasone; Cyclo, cyclophosphamide; R, lenalidomide maintenance; RZ, combination lenalidomide and vorinostat maintenance; KCRD, carfilzomib, cyclophosphamide, lenalidomide and dexamethasone; TE, transplant eligible; TNE, transplant non-eligible; REL, relapse (previously transplanted patients); NR, nonrandomised patients; MEL, melphalan; P, prednisolone; Pred, prednisolone; HDMP, High dose melphalan prednisolone; PV, vincristine prednisolone; C, cyclophosphamide; CCNU, Cyclophosphamide; Cyclo, Cyclophosphamide.

*Medical Research Council (MRC) trial.

†National Cancer Research Institute (NCRI) trial.

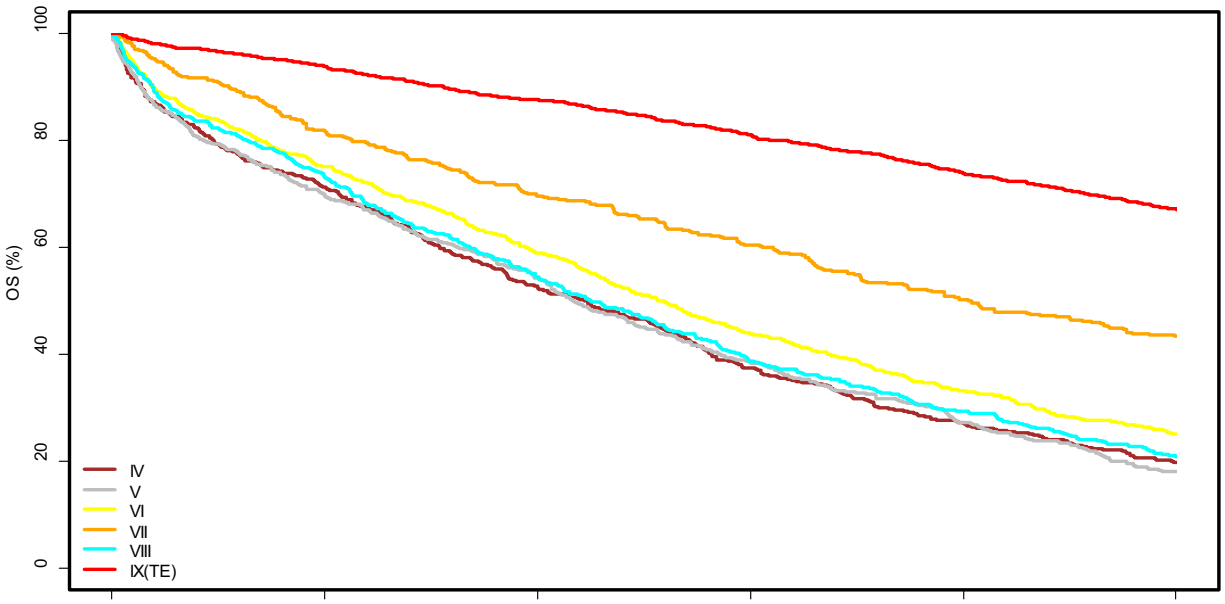
It was clear that alkylating agents were efficacious in MM and a major evolution of alkylator therapy came in the 1980s **with** Prof. Tim McElwain's seminal papers describing high-dose melphalan (HDMel: 100–140 mg/m^2) in MM, obtaining deep and lasting responses.[6,7] The main toxicity was profound myelosuppression of prolonged duration, leading to a procedural-related mortality of 20–25%. This resulted in the development of autologous stem cell support (ASCT) **to** allow safe delivery of HDMel, firstly with harvested bone marrow then subsequently cytokine-mobilised blood-derived stem cells in the 1990s.[8,9] Initially this was used to manage relapsed and refractory disease (RRMM) but efficacy was rapidly established in *de novo* disease in successive randomized trials. The first such study was carried out by the Intergroupe Francophone du Myelome (IFM) in the landmark IFM90 trial which showed a clear-cut benefit to the ASCT cohort.[10] Other research collaborative groups demonstrated a significant benefit in disease control (progression-free survival; PFS) but few demonstrated overall survival benefit (OS).[11,12] The issue was effectively settled by the large MRC Myeloma VII study led by Prof. Tony Child in which ABCM was compared to c-VAMP plus ASCT which showed convincing benefit in achieving complete response (CR), progression-free survival (PFS) and overall survival (OS).[13] With successive therapeutic advances (see below) ASCT has been tested for its relevance in the treatment algorithm and remains an important part of myeloma therapy as randomised clinical trials assessing new interventions against the addition of ASCT have resulted in superior PFS and/or OS for the ASCT strategy, despite the well-recognised long-term complications associated with HDMel.[14,15,16]

Allogenic transplantation (allo-SCT) has been performed in a small proportion of patients throughout this period but the potential benefits were marred by regimen-related toxicity and graft-*versus*-host disease in the pursuit of the putative graft-*versus*-myeloma effect.[17,18] However a limited number of studies have now been reported showing that the benefits of allo-SCT may be obtained by combining a reduced-intensity allo-SCT with a prior ASCT (auto–allo) thus reducing the transplant-related mortality, although benefit for the autoz–allo group only became obvious after five-year follow-up.[18,19] It is of interest that only now are we closer **to** harnessing a targeted immunotherapy-based therapeutic strategy in myeloma with the evolution of CAR T-cells and bi-specific T-cell engager (BiTE) technology in MM.

During the first decade of this century salvage ASCT (sASCT; defined as the use of a second ASCT after disease has progressed following a first, initial ASCT) was being used regularly in relapsed patients young and fit enough to undergo a repeat procedure, often with a variable length of first remission.[20,21] It became clear there was a need for robust clinical-trial-based evidence to establish if this was an appropriate therapeutic approach. The UKMF/BSBMT Myeloma X study defined that a sASCT not only improved the second-line PFS, it also augmented OS, with no significant cost in a patient's reported quality of life.[22,23,24] In the follow-up UKMRA Myeloma XII trial, now nearing completion of recruitment, patients relapsing after an initial ASCT receive a novel oral proteasome inhibitor (PI) and immunomodulatory drug (IMiD) combination (see below) before proceeding to a sASCT, with a randomization to standard HDMel or PI-augmented HDMel to augment depth of response (NCT03562169).

As well as ASCT the therapeutic landscape has changed within a generation, (revolution rather than evolution?) from the use of a single high dose of alkylating therapy **to** the widespread use of complex small molecules targeting intracellular signalling pathways and manipulating immune activation networks. The empirical cytotoxic therapy of the last century has mostly given way, firstly to therapy directed at known intracellular pathways, for example PIs (the proteosome), Imids (multiple targets) and histone deacetylase inhibitors (HDACs, e.g. pabinostat). In the last decade we have witnessed the identification of specific surface and intracellular targets with the development of agents to specifically target them, for example, CD38 – daratumumab; Exportin-1 (XPO1) – selinixor[25] and B-cell maturation antigen (BMCA) – GSK2857916 antibody-drug conjugate.[26] Figure 1 illustrates the gain in OS obtained by incorporation of newer agents into successive MRC trials.[27] While much of the development of these new agents has taken place in the USA, the United Kingdom has been involved through British scientists working both in the United Kingdom and abroad, and also through clinical trial participation in all the major licensing trials, for example Apex – bortezomib[28]; MM003 – lenalidomide[29]; Pollux – daratumumab plus lenalidomide[30]; Castor – daratumumab plus bortezomib[31]; Tourmaline[32] – elotuzumab[33] and Eloquent – ixazomib.[34]

This dramatic change in the treatment algorithm over the last two decades started with the discovery of the anti-MM effect of thalidomide when it was empirically tested in RRMM.[35] This discovery of a 'new class' of drugs led to efforts to really understand the underlying biology behind thalidomide's anti-MM effect and to develop safer and more potent versions of thalidomide. These agents are now referred to as IMiDs.[36] Thalidomide very quickly became a front-line agent, and the NCRI Myeloma IX was the large phase III study that demonstrated the impact of replacing infusional chemotherapy with thalidomide plus steroids and cyclophosphamide (CTD).[37,38,39] However, the vast majority of MM patients **still** relapse, and the search for further novel agents continued. With the introduction of the first in class PI, bortezomib, in 2003 anti-MM therapy entered the age of sub-cellular pathway targeted therapy. The UK contributed significantly during the clinical development of bortezomib, but of particular note was Prof. Jamie Cavenagh's inspirational blending of the *old and the new*, substituting bortezomib for vincristine in the VAD-like schedule [PAD: bortezomib (PS341) adriamycin and dexamethasone]. This regime was highly effective in newly diagnosed patients as



OS Estimate [95%CI]					
IV	71·3 [67·5, 75·2]	52·6 [48·5, 57]	37·4 [33·5, 41·7]	27·1 [23·6, 31·2]	19·7 [16·6, 23·4]
V	69·5 [66·2, 73·1]	54·2 [50·6, 58·1]	38·5 [35, 42·3]	27·1 [24, 30·7]	18 [15·3, 21·1]
VI	75 [72·4, 77·8]	58·9 [55·9, 62]	43·8 [40·8, 46·9]	33·1 [30·3, 36·2]	25·1 [22·5, 27·9]
VII	81·5 [77·8, 85·4]	69·6 [65·2, 74·2]	60·3 [55·7, 65·3]	50·1 [45·4, 55·3]	43·3 [38·7, 48·5]
VIII	73 [69·5, 76·7]	54·4 [50·5, 58·6]	38·7 [34·8, 42·9]	29·2 [25·6, 33·3]	20·9 [17·6, 24·7]
IX(TE)	93·8 [92·6, 95]	87·5 [85·8, 89·2]	80·9 [78·9, 82·9]	73·7 [71·5, 76]	67·1 [64·7, 69·6]

Fig 1. Overall survival of patients admitted into successive MRC/NCRI clinical trials.

well as being effective in relapsed patients and was incorporated into the NCRI Myeloma X trial for sASCT at first relapse.[40,41,42,23]

Lenalidomide, the first of the second-generation IMiDs, demonstrated significant efficacy, especially with dexamethasone, without the quality of life-limiting side effects of thalidomide and became established as treatment for RRMM and subsequently a front-line therapy for ASCT-ineligible patients.[29,43,44] As well as being involved in the global regulatory studies, the UK contributed to the efficacy data through the NCRI Myeloma XI trial, led by Prof. Graham Jackson. This was the largest front-line study in MM ever, successfully defining the role of lenalidomide maintenance.[45] The UK has been involved in the clinical development pathways of the other second-generation (pomalidomide) and third-generation IMiDs.[46,47,48,36,49]

The breakthrough therapeutic development of note in the current decade has been the development and licensing of the monoclonal antibody that targets CD38-expressing cells, daratumumab.[50] Though there is modest single-agent activity, the combination of daratumumab with PIs and IMiDs has seen some remarkable efficacy signals in clinical trials, initially in RRMM but also in front-line therapy[30,51,52,31]. Currently, there are some 50–60 agents being actively investigated in clinical trials, many with diverse mechanisms of action and distinct targets, including cellular therapies, monoclonal antibodies, small molecules (such as venetoclax and the nuclear transport inhibitor selinexor) and now immunotherapies [CAR T cells, BiTE, CAR NK (natural killer] cells] are being investigated.[53,54,55]

Biomarker discovery

As a consequence of a very successful clinical trials portfolio and allied translational work, researchers in MM have been able to define *predictive* biomarkers, and the United Kingdom has been at the forefront, in particular in the arena of genomic risk biomarkers, minimal residual disease (MRD) detection and clinical frailty scores.

MM is a genetically complex disease that develops in a multistep process with the primary genetic events including chromosomal translocations involving the immunoglobulin heavy-chain genes (IGH) and aneuploidy with subsequent, secondary genetics events including copy number abnormalities, DNA hypomethylation and acquired mutations leading to tumour progression.[56] Since the early 2000s there has been an exponential growth of knowledge pertaining to genomic and molecular characterisation of MM with the technical advances from metaphase karyotyping **and** fluorescent *in situ* hybridisation (FISH) to more high-throughput technologies

such as gene expression profiling (GEP), next generation sequencing (NGS), whole genome and whole exome sequencing, leading to a better appreciation of MM biology and its implications in therapy.[57]

Using FISH, the primary genetic abnormalities in MM include translocations primarily involving the IgH gene locus on chromosome 14 (14q32.33) with one of several partner chromosomes including chromosomes 4, 6, 11, 14 and 20.[57] With the exception of t(11;14), these balanced translocations confer a poorer outcome with therapy.[58] The deletion of chromosome 17p, affecting the tumour suppressor gene, *TP53*, has been highlighted as adversely affecting survivorship.[59] More recently abnormalities of chromosome 1 have been defined as a genetic risk adversely affecting survivorship, especially del 1p and gain 1q. Moreover, MM displays significant clonal heterogeneity which can impact presentation and drug sensitivity, durability of response to modern therapies and most importantly survivorship.[60]

The use of trial-based sampling with associated clinical outcome data has advanced our understanding in the biology of MM and has been critical to assess its true impact. Here, the United Kingdom has led the field, through the work of Prof. Fiona Ross, Prof. Gareth Morgan and latterly, Dr Martin Kaiser using samples and outcome data from the large frontline phase III trials conducted in the UK (Myeloma VII, IX, X and XI).[61,62,63] The collective evidence has highlighted the predictive biomarker status of genetic aberrations, and has defined three categories of risk: standard risk, high risk (one of the above-mentioned lesions) and ultra-high risk (two or more lesions) with a clear-cut influence on PFS and OS.[64]

Response biomarkers have become more important over the last two decades with the advent of more targeted and effective anti-MM therapies. It is increasingly recognised that the deeper the response to treatment, the more durable the effect, possibly even affecting survivorship.[65] However, where once attaining a CR was the aim of therapy, more recently becoming MRD-negative (a deeper response than CR) is associated with even better outcomes, hence MRD detection has become increasingly important. Advances in technology, from the improvements in the sensitivity of flow cytometery (MFC) to detect small populations of malignant cells (from 10^{-4} to 10^{-6}) to the utility and practical delivery of NGS to provide a molecular basis for MRD, has focused clinical attention on measurement of MRD and provided new therapeutic goals.[66,67,68] Arguably, the largest clinical dataset reflecting the impact of MRD detection by MFC has been generated by Dr Roger Owen and Dr Andy Rawstron from the large front-line phase III trials conducted in the United Kingdom (Myeloma VII, IX and XI).[69,70,71] Achievement of MRD-negative status following treatment is associated with a significant improvement in PFS and OS.[72] This large-cohort meta-analysis identified MRD status as a marker of long-term survival outcome in patients with MM, establishing it as a suitable predictive biomarker in MM and an appropriate end-point in clinical trials.

Patients with MM are at risk of therapy-related toxicity, particularly the transplant non-eligible (TNE), as a result of the complex interplay of age, physical function, cognitive function and comorbidity. The International Myeloma Working Group proposed a scoring system (IMWG FS) for MM patient frailty that predicts survival, adverse events and treatment tolerability using age, the Katz Activity of Daily Living (ADL), the Lawton Instrumental Activity of Daily Living (IADL) and the Charlson Comorbidity Index (CCI), which was tested and validated in clinical-trial populations.[73] The UKMRA generated a more laboratory-based objective risk score incorporating age, PS, CRP and ISS which was able to discriminate not only therapy-related toxicity and regimen completion but survivorship and impact on quality of life.[74] Although more of a risk score than a traditional frailty score, it nonetheless defined patient populations who are vulnerable in the treatment setting. It has also been tested and validated in clinical trial populations and has since been replicated in a real-world setting.[75]

Supportive care

While much has been achieved in anti-MM therapy, the role of supportive care has also evolved. Almost one in three MM patients present as emergencies with advanced disease causing serious morbidity.[76] The sequelae may be renal failure and/or hypercalcaemia for which prompt therapy is beneficial to acute presentations but a significant proportion develop chronic kidney disease.[77] One of the earliest findings from the MRC studies was that maintaining good hydration could improve renal health and certainly help to prevent further renal deterioration.[78] Indeed, the advice to drink 3 l of fluid per day is still relevant and useful today. The United Kingdom has **also** been pivotal in demonstrating the benefit of bisphosphonates in the management of myeloma bone disease initially through the work of Prof. Graham Russell[79] and in studies linked to the MRC/NCRI trials, the benefits of clodronate[80,81] and subsequently zolodronic acid,[82,83] now accepted internationally as a standard of care. Unfortunately, we remain (as yet) unable to promote healing of these lesions. Erythropoietin is now accepted for therapy-induced anaemia but no remedy has been found for the fatigue which often accompanies effective therapy with IMiDs and other novel agents. Despite extensive use of systemic anticoagulants thromboembolic events remain a problem particularly in IMiD-treated patients.[84] Happily, despite the trend to ever more intensive therapy quality of life does not appear to be adversely affected.[22,85] Longer survivals have meant that extra-medullary disease (EMD) is seen more often, usually as a late finding, often containing a new clone of the disease, and these progressions are frequently difficult to manage.[86,87] Particularly in older/frail patients, early death remains a problem, most commonly as a consequence of infection.[74] The UK TEAMM trial has demonstrated the benefit of prophylactic antibiotics in the early months of treatment and

this approach needs to be incorporated into routine management.[88]

Collaborative working

The pace of scientific and therapeutic discovery has increased exponentially over the past two decades and has necessitated working more actively and collaboratively by myeloma professionals. Started by a small group of myeloma enthusiasts and under first the chairmanship of Prof. Tony Child followed by Dr Diana Sampson and then Dr Steve Schey the UK Myeloma Forum is a group for medical, nursing, scientific and other professionals working in the field of myeloma. It has established two regular high-quality one-day meetings per year with an endowment facilitating speakers from Europe and North America. It actively promoted the existing MRC/NCRI trials but recognising the lack of Phase 2 trials and the associated access to new therapeutic agents, and working with Eric Low of the patient support group, Myeloma United Kingdom (MUK), we established the MUK early trials portfolio which supported 10 Phase I and II studies (Table II). From its early days UKMF has also been active in producing high-quality evidence-based guidelines on a range of myeloma topics. This has reflected the collegial and inclusive nature of the UK myeloma community. These guidelines, all adopted by the British Society for Haematology and published in this journal, have been an effective form of training and basis of good practise for haematologists in the United Kingdom and beyond.[89,90,91,92,93] In addition UKMF members have played an important role in the development of the National Institute for Health Care Excellence (NICE) guidelines for the management of myeloma [NICE guideline (NG35)].[94] More recently the UKMF has worked with MUK to ensure that the patient voice is heard clearly with respect to NICE determinations on the availability of novel therapeutic agents, although the cost of these agents often means that UK clinicians are unable to offer therapy seen as optimal. This active role in advocacy started with our support of the successful MUK appeal against the initial decision of NICE to not recommend the use of bortezomib for relapsed patients. In the years since that time and with the arrival of an expanding portfolio of novel agents for myeloma this advocacy on behalf of MM patients has become a major part of the work of UKMF.

Current status and future directions

As a consequence of the therapeutic revolution in MM, the cohesive and inclusive working of clinical trialists and translation academic **clinic**ians and scientists is key. At a national level, we established the UK Myeloma Research Alliance (UKMRA) through which our portfolio of clinical studies is developed and delivered including the early-phase studies previously supported by MUK. The UKMRA activity continues to thrive, with a *run-through* research strategy (early-phase trials to inform late-phase trials) utilising its Concept and Access Research Programme (CARP) accelerated trials platform (funded by Myeloma UK). As part of this strategy, we have incorporated our biomarker research to date into the design of the trials to develop these from *prognostic* to *predictive* biomarkers leading to adoption for everyday clinical use.

Many collaborative study groups as well as industry-driven regulator clinical trials have defined the prognostics impact of high-risk genetics.[95,96] However, managing these patients has yet to see a stepwise breakthrough in therapy delivery and outcomes. Dr Martin Kaiser and Dr Matt Jenner are leading the delivery of a novel study, the MUK9 OPTIMUM trial, where newly diagnosed patients are being screened in rapid real-time to define a molecularly high-risk population and then to enrol these patients into a dose-dense delivery schedule (NCT03188172). This proof-of-concept trial aims to use well-established genomic prognostic biomarkers and move to the next level and thus define it as a predictive biomarker to direct therapy. Moving forward with the clinically challenging high-risk patients, we now enter a time of immunotherapy, with monoclonal antibodies, CAR T-cells and BiTE technologies that may bring hope of parity of outcomes between standard and high-risk disease.[97,98]

Table II. Summary of myeloma UK phase 1 and 2 trials.

Trial	Investigational agent	Phase	Status	Recruitment	Pharma partner	Reference
MUK1	Bendamustine, thalidomide, dexamethasone	2a	Closed	98	Napp	Schey S et al.[99]
MUK3	Pabinostat/tosedostat	1b	Closed	36	Chroma	Popat R et al.[100]
MUK4	Vorinostat	2	Closed	16	Merck	Jenner et al.[101]
MUK5	Carfilzomib, cyclophosphamide, dexamethasone	2b	Closed	300	Amgen	Yong K et al.[101]
MUK6	Pabinostat, bortezomib, thalidomide, dexamethasone	2	Closed	54	Novartis	Popat et al.(a & b) [102,103]
MUK7	Pomalidomide, cyclophosphamide, dexamethasone	2b	Closed	102	Celgene	Croft J et al.[104]
MUK8	Ixazomib, cyclophosphamide, dexamethasone	2b	Closed	112	Takeda	Hinsley et al.[105]
MUK9	Daratumumab, bortezomib, lenalidomide, dexamethasone	2	Closed	Screened 472 Randomised 108	Janssen/ Celgene	Shah V et al.[59]
MUK11	Reolysin	2a	Closed	3	Celgene	
MUK12	Selinixor, cyclophosphamide, dexamethasone	2	Open		Karyopharm	

Current and proposed studies

As highlighted, the United Kingdom has been at the forefront of assessing and validating MRD as a prognostic biomarker. The United Kingdom is leading international research to define the role of predictive biomarkers in the UKMRA Myeloma XV (RADAR) study (CI: Prof. Kwee Yong and Prof. Mark Cook). Patients rendered MRD-negative through induction/ASCT will be studied to define whether a de-escalation of post-transplant therapy is safe and effective whereas those who remain MRD-positive post-ASCT will be studied for the impact of treatment escalation, including immunotherapy. The study aims to open for recruitment in Q3/4 of 2020.

It is clear from frailty clinical scores and biomarker research that there is a clear unmet need in assessing how to deliver the optimum treatment for TNE MM patients. The UK Myeloma Research Alliance (UKMRA) has developed the Myeloma XIV: FITNESS study (NCT03720041; CI Prof. Graham Jackson and Prof. Gordon Cook) where patients will be randomised to a *treatment-adaptive* arm with therapy being dose-reduced in accordance with the IMWG FS compared to a conventional *treatment-reactive* arm where therapy will be modified in relation to toxicity and tolerance (https://clinicaltrials.gov/ct2/show/NCT03720041?cond=myeloma+XIV&draw=2&rank=1). The aim of the study will be the prevention of treatment discontinuation and reduction of early death as well as defining the impact on PFS and survivorship. Funded by Cancer Research UK, the trial has opened for recruitment in July 2020. This is one approach to the use of frailty scores and there are currently seven other frailty-associated trials in MM listed on clintrials.gov either recruiting or in set-up (https://clinicaltrials.gov/ct2/results?cond=Myeloma&term=frailty&cntry=&state=&city=&dist=).

Conclusion

Throughout history, the *evolution* of medicine has been typified by the advancement in biological knowledge at a pace considerably ahead of therapeutic developments. In MM, in the last two decades, the *revolution* has been a reversal of this, in that therapeutic advances have led the biological discoveries, and inspired the bench-to-bedside-and-back ethos. The UK has played an important and central role in this revolution and continues to contribute quality clinical and scientific research that is primarily patient-facing, informing practice and improving outcome.

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Conflicts of interest

GC – Honoraria: Amgen, Bristol-Myers Squibb, Celgene, Janssen, Sanofi, Karyopharm and GSK; Research funding: Celgene, Janssen, Takeda. TCMM – None.

References

1. Solly S. Remarks on the pathology of Mollities Ossium with cases. *Medico-chir trans Lond*. 1844;**27**:435–61.
2. Podar K, Tai YT, Hideshima T, Vallet S, Richardson PG, Anderson KC. Emerging therapies for multiple myeloma. *Expert Opin Emerg Drugs*. 2009;**14**:99–127.
3. Kyle RA, Steensma DP. History of multiple myeloma. *Recent Results Cancer Res*. 2011;**183**:3–23-1.
4. Child AJ. Evolving strategies for the treatment of myelomatosis. *Br J Haematol*. 1994;**88**:672–8.
5. MacLennan I, Chapman C, Dunn J, Kelly K; for the Medical Research Council Working Party For Leukæmia In Adults. Combined chemotherapy with ABCM versus melphalan for treatment of myelomatosis. *Lancet*. 1992;**339**:200–5.
6. McElwain TJ, Powles RL. High dose intravenous melphalan for plasma cell leukaemia and myeloma. *Lancet*. 1983;**322**:822–4.
7. Selby PJ, McElwain TJ, Nandi AC, Perren TJ, Powles RL, Tillyer CR, *et al.* Multiple myeloma treated with high dose intravenous melphalan. *Br J Haematol*. 1987;**86**:55–62.
8. Cook G, Marinaki P, Farrell E, Pearson C, Alcorn MJ, Sharp RA, *et al.* Peripheral blood progenitor cell mobilisation in patients with multiple myeloma following oral idarubicin and dexamethasone (Z-Dex) induction therapy. *Leukaemia*. 1997;**11**(Suppl. 5):535–45.
9. Körbling M, Freireich EJ. Twenty-five years of peripheral blood stem cell transplantation. *Blood*. 2011;**117**:6411–6.
10. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, *et al.* A prospective, randomised trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med*. 1996;**335**:91–7.
11. Fermand JP, Ravaud P, Chevret S, Divine M, Leblond V, Belanger C, *et al.* High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: Up-front or rescue treatment? Results of a multicentre sequential randomised clinical trial. *Blood*. 1998;**92**:3131–6.
12. Tricot G, Jagannath S, Vesole D, Nelson J, Tindle S, Miller L, *et al.* Peripheral blood stem cell transplants for multiple myeloma: Identification of favorable variables for rapid engraftment in 225 patients. *Blood*. 1995;**85**:588–96.
13. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, *et al.* High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003;**348**:1875–83.
14. Attal M, Lauwers-Cances V, Hulin C, Leleu X, Caillot D, Escoffre M, *et al.*; for the IFM 2009 Study. Lenalidomide, bortezomib and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;**376**:1311–20.
15. Mina R, Petrucci MT, Corradini P, Spada S, Patriarca F, Cerrato C, *et al.* Treatment intensification with autologous stem cell transplantation and lenalidomide maintenance improves survival outcomes of patients with newly diagnosed multiple myeloma in complete response. *Clin Lymphoma Myeloma Leuk*. 2018;**18**:533–40.
16. Cavo M, Gay F, Beksac M, Pantani L, Petrucci MT, Dimopoulos MA, *et al.* Autologous haematopoietic stem-cell transplantation versus bortezomib–melphalan–prednisone, with or without bortezomib–lenalidomide–dexamethasone consolidation therapy, and lenalidomide

maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. *Lancet Haematol*. 2020;**7**:456–68.
17. Cook G, Bird JM, Marks DI. In pursuit of the allo-immune response in multiple myeloma: where do we go from here? *Bone Marrow Transplant*. 2009;**43**:91–9.
18. Gahrton G, Iacobelli S, Björkstrand B, Hegenbart U, Gruber A, Greinix H, *et al.* Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: Long-term results of the EBMT-NMAM2000 study. *Blood*. 2013;**121**:5055–63.
19. Bruno B, Rotta M, Patriarca F, Mordini N, Bernardino A, Carnevale-Schianca F, *et al.* A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med*. 2007;**382**:1800–10.
20. Morris C, Iacobelli S, Brand R, Bjorkstrand B, Drake D, Niederwieser D, *et al.* Benefit and timing of second transplantations in multiple myeloma: clinical findings and methodological limitations in a European Group for Blood and Marrow registry study. *J Clin Oncol*. 2004;**22**:1674–81.
21. Cook G, Liakopoulou E, Pearce R, Cavet J, Morgan GJ, Kirkland K, *et al.* Factors influencing the outcome of a second autologous stem cell transplant (ASCT) in relapsed multiple myeloma: a study from the British society of blood and marrow transplantation registry. *Biol Blood Marrow Transplant*. 2011;**17**:1638–45.
22. Ahmedzai SH, Snowden JA, Ashcroft AJ, Cairns DA, Williams C, Hockaday A, *et al.* Patient-reported outcome results from the open-label, randomised phase III myeloma X trial evaluating salvage autologous stem-cell transplantation in relapsed multiple myeloma. *J Clinl Oncol*. 2019;**37**:1617–29.
23. Cook G, Williams C, Brown JM, Cairns DA, Cavenagh J, Snowden JA, *et al.* High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label. *Lancet Oncol*. 2014;**15**:874–85.
24. Cook G, Ashcroft AJ, Cairns DA, Williams CD, Brown JM, Cavenagh JD, *et al.* The effect of salvage autologous stem-cell transplantation on overall survival in patients with relapsed multiple myeloma (final results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2016;**3**:e340–e351.
25. Syed YS. Selinixor: first global approval. *Drugs*. 2019;**79**:1485–95.
26. Trudel S, Lendvai N, Popat R, Voorhees PM, Reeves B, Libby EN, *et al.* Targeting B-cell maturation antigen with GSK2857916 antibody-drug conjugate in relapsed or refractory multiple myeloma (BMA117159): a dose escalation and expansion phase 1 trial. *Lancet Oncol*. 2018;**12**:1641–53.
27. Cairns D, Gregory W, Dunn J, Iqbal G, MacLennan I, Rawstron A, *et al.* From plateau to MRD-Negative CR: outcomes in the MRC/NCRI series of randomised trials in newly diagnosed patients with multiple myeloma from 1980 to 2016. *Clin Lymphoma Myeloma Leuk*. 2016;**17**:e60.
28. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, *et al.*; Assessment of proteasome inhibition for extending remissions (APEX) investigators. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2005;**352**:2487–98.
29. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, *et al.* Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;**357**:2123–32.
30. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, *et al.* Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;**375**:1319–31.
31. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, *et al.* Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;**375**:754–66.
32. Dimopoulos MA, Gay F, Schjesvold F, Beksac M, Hajek R, Weisel KC, *et al.* Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet*. 2019;**393**:253–64.
33. Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, *et al.*; TOURMALINE-MM1 Study Group. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;**374**(17):1621–34.
34. Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka W-C, *et al.* Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med*. 2015;**373**:621–31.
35. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, *et al.* Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med*. 1999;**341**:1565–71.
36. Holstein SA, McCarthy PL. Immunomodulatory drugs in multiple myeloma: mechanisms of action and clinical experience. *Drugs*. 2017;**77**:505–20.
37. Morgan GJ, Davies FE, Gregory WM, Russell NH, Bell SE, Szubert AJ, *et al.* Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. *Blood*. 2011;**118**(5):1231–8.
38. Morgan GJ, Davies FE, Gregory WM, Bell SE, Szubert AJ, Coy NN, *et al.* Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomised trial results. *Haematologica*. 2012;**97**:442–50.
39. Morgan GJ, Gregory WM, Davies FE, Bell SE, Szubert AJ, Brown JM, *et al.* The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. *Blood*. 2012;**119**:7–15.
40. Cavenagh JD, Popat R, Curry N, Stec J, Morris TC, Drake M, *et al.* PAD combination therapy (PS-341/Bortezomib, Adriamycin and Dexamethasone) for previously untreated patients with multiple myeloma. *Blood*. 2004;**104**:1478.
41. Oakervee HE, Popat R, Curry N, Smith P, Morris C, Drake M, *et al.* PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. *Br J Haematol*. 2005;**129**:755–62.
42. Morris C, Cook G, Streetly M, Kettle P, Drake M, Quinn M, *et al.* Re-transplantation after bortezomib-based therapy. *Br J Haematol*. 2011;**153**:666–8.
43. Facon T, Dimopoulos MA, Dispenzieri A, Catalano JV, Belch A, Cavo M, *et al.* Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. *Blood*. 2018;**131**:301–10.
44. Zeldis JB, Knight R, Hussein M, Chopra R, Muller G. A review of the history, properties, and use of the immunomodulatory compound lenalidomide. *Annals N Y Acad Sci*. 2011;**1222**:76–82.
45. Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C, *et al.* 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**:57–73.
46. Schey SA, Fields P, Bartlett JB, Clarke IA, Ashan G, Knight RD, *et al.* Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. *J Clin Oncol*. 2004;**16**:3269–76.
47. Streetly MJ, Gyertson K, Daniel Y, Zeldis J, Kazmi M, Schey SA. Alternate day pomalidomide retains anti-myeloma effect with reduced adverse events and evidence of in vivo immunomodulation. *Br J Haematol*. 2008;**141**:41–51.
48. Bjorklund CC, Kang J, Amatangelo M, Polonskaia A, Katz M, Chiu H, *et al.* Iberdomide (CC-220) is a potent cereblon E3 ligase modulator with antitumor and immunostimulatory activities in lenalidomide- and pomalidomide-resistant multiple myeloma cells with dysregulated CRBN. *Leukemia*. 2020;**34**:1197–201.
49. Miguel JS, Weisel K, Moreau P, Lacy M, Song K, Delforge M, *et al.* Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;**14**:1055–66.
50. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, *et al.* Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med*. 2015;**373**:1207–19.

51. Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, *et al.* Daratumumab plus lenalidomide and dexamethasone for untreated Myeloma. *N Engl J Med*. 2019;**380**:2104–15.
52. Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, *et al.* Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *N Engl J Med*. 2018;**378**:518–28.
53. Bertamini L, Bonello F, Boccadoro M, Bringhen S. New drugs in early development for treating multiple myeloma: all that glitters is not gold. *Expert Opin Investig Drugs*. 2020;**20**:989–1004.
54. Nijhof IS, van de Donk NWCJ, Zweegman S, Lokhorst HM. Current and new therapeutic strategies for relapsed and refractory multiple myeloma: an update. *Drugs*. 2018;**78**:19–37.
55. Cook G, Zweegman S, Mateos M-V, Suzan F, Moreau P. A question of class: treatment options for patients with relapsed and/or refractory multiple myeloma. *Crit Rev Oncol/Hematol*. 2018;**121**:74–89.
56. Solimando AG, Da Vià MC, Cicco S, Leone P, Di Lernia G, Giannico D, *et al.* High-risk multiple myeloma: integrated clinical and omics approach dissects the neoplastic clone and the tumor microenvironment. *J Clin Med*. 2019;**8**:996–1022.
57. Barwick BG, Gupta VA, Vertino PM, Boise LH. Cell of origin and genetic alterations in the pathogenesis of multiple myeloma. *Front Immunol*. 2019;**10**:1121.
58. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2020;**95**:548–67.
59. Boyd KD, Ross FM, Tapper WJ, Chiecchio L, Dagrada G, Konn ZJ, *et al.* The clinical impact and molecular biology of del(17p) in multiple myeloma treated with conventional or thalidomide-based therapy. *Genes Chromosomes Cancer*. 2011;**50**:765–74.
60. Pawlyn C, Morgan GJ. Evolutionary biology of high-risk multiple myeloma. *Nat Rev Cancer*. 2017;**17**:543–56.
61. Cook G, Royle KL, O'Connor S, Cairns DA, Ashcroft AJ, Williams CD, *et al.* The impact of cytogenetics on duration of response and overall survival in patients with relapsed multiple myeloma (long-term follow-up results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. *Br J Haematol*. 2019;**185**:450–67.
62. Ross FM, Chiecchio L, Dagrada G, Protheroe RKM, Stockley DM, Harrison CJ, *et al.* The t(14;20) is a poor prognostic factor in myeloma but is associated with long-term stable disease in monoclonal gammopathies of undetermined significance. *Haematologica*. 2010;**95**:1221–5.
63. Walker BA, Boyle EM, Wardell CP, Murison A, Begum DB, Dahir NM, *et al.* Mutational spectrum, copy number changes, and outcome: Results of a sequencing study of patients with newly diagnosed myeloma. *J Clin Oncol*. 2015;**33**:3911–20.
64. Shah V, Sherborne Al, Walker Ba, Johnson Dc, Boyle Em, Ellis S, *et al.* Prediction of outcome in newly diagnosed myeloma: a meta-analysis of the molecular profiles of 1905 trial patients. *Leukemia*. 1905;**32**: 102–10.
65. Harousseau JL, Attal M, Avet-Loiseau H. The role of complete response in multiple myeloma. *Blood*. 2009;**114**:1339–3146.
66. Demaree A, Hewitt A, Lee LW, Eckert B. Real-world sustained minimal residual disease (MRD) negativity using NGS in multiple myeloma. *J Clin Oncol*. 2020;**38**(15_suppl):e19280.
67. Flores-Montero J, Sanoja-Flores L, Paiva B, Puig N, García-Sánchez O, Böttcher S, *et al.* Next Generation Flow for highly sensitive and standardized detection of minimal residual disease in multiple myeloma. *Leukemia*. 2017;**31**:2094–103.
68. Landgren O, Devlin S, Boulad M, Mailankody S. Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis. *Bone Marrow Transplant*. 2016;**51**(12):1565–8.
69. De Tute RM, Rawstron AC, Gregory WM, Child JA, Davies FE, Bell SE, *et al.* Minimal residual disease following autologous stem cell transplant in myeloma: impact on outcome is independent of induction regimen. *Haematologica*. 2016;**101**:e69–e71.
70. Rawstron AC, Child JA, De Tute RM, Davies FE, Gregory WM, Bell SE, *et al.* Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: Impact on outcome in the Medical Research Council Myeloma IX study. *J Clin Oncol*. 2013;**31**:2540–7.
71. Rawstron AC, Gregory WM, De Tute RM, Davies FE, Bell SE, Drayson MT, *et al.* Minimal residual disease in myeloma by flow cytometry: independent prediction of survival benefit per log reduction. *Blood*. 2015;**125**:1932–5.
72. Munshi NC, Avet-Loiseau H, Rawstron AC, Owen RG, Child JA. Minimal residual disease predicts superior survival in patients with multiple myeloma: a meta-analysis. *JAMA Oncol*. 2017;**3**:28–35.
73. Palumbo A, Bringhen S, Mateos MV, Larocca A, Facon T, Kumar SK, *et al.* Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood*. 2015;**125**:2068–74.
74. Cook G, Royle KL, Pawlyn C, Hockaday A, Shah V, Kaiser MF, *et al.* A clinical prediction model for outcome and therapy delivery in transplant-ineligible patients with myeloma (UK Myeloma Research Alliance Risk Profile): a development and validation study. *Lancet Haematol*. 2019;**6**: E154–E166.
75. Redder L, Klausen TW, Vangsted AJ, Gregersen H, Andersen NF, Pedersen RS, *et al.* Validation of a New Clinical Prediction Model for outcome in newly diagnosed multiple myeloma patients not eligible for autologous stem-cell transplantation; a Population-Based Study from the Danish National Multiple Myeloma Registry. *Blood*. 2019;**134**(Suppl. 1):1849.
76. Koshiaris C, Oke J, Abel L, Nicholson BD, Ramasamy K, Van Den Bruel A. Quantifying intervals to diagnosis in myeloma: a systematic review and meta-analysis. *B Med J Open*. 2018;**8**:e019758.
77. Leung N, Nasr SH. Myeloma-related kidney disease. *Adv Chronic Kidney Disease*. 2014;**21**:36–47.
78. Medical Medical Research Council Working Party on Leukaemia in Adults. Analysis and management of renal failure in fourth MRC myelomatosis trial. *Br Med J*. 1984;**288**:1411–6.
79. Russell RG. Bisphosphonates: from bench to bedside. *Annals N Y Acad Sci*. 2006;**1068**:367–401.
80. McCloskey EV, MacLennan IC, Drayson MT, Chapman C, Dunn J, Kanis JA. A randomised trial of the effect of clodronate on skeletal morbidity in multiple myeloma. MRC Working Party on Leukaemia in Adults. *Br J Haematol*. 1998;**100**:317–25.
81. McCloskey EV, Dunn JA, Kanis JA, MacLennan IC, Drayson MT. Long term follow-up of a prospective, double-blind, placebo-controlled *randomized* trial of clodronate in multiple myeloma. *Br J Haematol*. 2001;**113**:1035–43.
82. Morgan GJ, Child JA, Gregory WM, Szubert AJ, Cocks K, Bell SE, *et al.* Effects of zoledronic acid versus clodronic acid on skeletal morbidity in patients with newly diagnosed multiple myeloma (MRC Myeloma IX): secondary outcomes from a randomised controlled trial. *Lancet Oncol*. 2011;**12**:743–52.
83. Morgan GJ, Davies FE, Gregory WM, Bell SE, Szubert AJ, Cook G, *et al.* Long-term follow-up of MRC Myeloma IX trial: Survival outcomes with bisphosphonate and thalidomide treatment. *Clin Cancer Res*. 2013;**19**:6030–8.
84. Bradbury CA, Craig Z, Cook G, Pawlyn C, Cairns DA, Hockaday A, *et al.* Thrombosis in patients with myeloma treated in the Myeloma IX and Myeloma XI phase 3 randomized controlled trials. *Blood*. 2020;**136**:1091–104.
85. Royle K-L, Gregory WM, Cairns DA, Bell SE, Cook G, Owen RG, *et al.* Quality of life during and following sequential treatment of previously untreated patients with multiple myeloma: findings of the Medical Research Council Myeloma IX randomised study. *Br J Haematol*. 2018;**182**:816–29.
86. Jagosky MH, Usmani SZ. Extramedullary disease in multiple myeloma. *Curr Hematol Malig Rep*. 2020;**15**:62–71.
87. Varga C, Xie W, Laubach J, Ghobrial IM, O'Donnell EK, Weinstock M, *et al.* Development of extramedullary myeloma in the era of novel agents: no evidence of increased risk with lenalidomide-bortezomib combinations. *Br J Haematol*. 2015;**169**:843–50.

88. Drayson MT, Bowcock S, Planche T, Iqbal G, Pratt G, Yong K, *et al.* Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet Oncol*. 2019;**20**:1760–72.
89. Bird JM, Owen RG, D'Sa S, Snowden JA, Pratt G, Ashcroft J, *et al.* Guidelines for the diagnosis and management of multiple myeloma. *Br J Haematol*. 2011;**154**:32–75.
90. Pratt G, Jenner M, Owen R, Snowden JA, Ashcroft J, Yong K, *et al.* Updates to the guidelines for the diagnosis and management of multiple myeloma. *Br J Haematol*. 2014;**167**:131–3.
91. Snowden JA, Ahmedzai SH, Ashcroft JA, D'Sa S, Littlewood T, Low E, *et al.* Guidelines for supportive care in multiple myeloma 2011. *Br J Haematol*. 2011;**154**:76–103.
92. Snowden JA, Greenfield DM, Bird JM, Boland E, Bowcock S, Fisher A, *et al.*; UK Myeloma Forum (UKMF) and the British Society for Haematology (BSH). Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. *Br. J. Haematol.*. 2017;**176**:888–907.
93. Chantry A, Kazmi M, Barrington S, Goh V, Mulholland N, Streetly M, *et al.*; British Society for Haematology Guidelines. Guidelines for the use of imaging in the management of patients with myeloma. *Br J Haematol*. 2017;**178**:380–93.
94. Pratt G, Morris TC. Review of the NICE guidelines for multiple myeloma. *Int J Lab Haematol*. 2017;**39**:1–11.
95. Rajkumar SV. Multiple myeloma: 2018 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2018;**93**:1091–110.
96. Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, Anderson KC, *et al.* Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood*. 2016;**127**:2955–62. https://doi.org/10.1182/blood-2016-01-631200
97. Gay F, Engelhardt M, Terpos E, Wäsch R, Giaccone L, Auner HW, *et al.* From transplant to novel cellular therapies in multiple myeloma: European myeloma network guidelines and future perspectives. *Haematologica*. 2018;**103**(2):197–211.
98. Hudecek M, Einsele H. Myeloma CARs are rolling into the clinical arena. *Blood*. 2016;**128**:1667–8.
99. Schey S, Brown S, Tillotson AL, Yong K, Williams C, Davies F, *et al.*; on behalf of the Myeloma UK Early Phase Clinical Trial Network. Identifying a tolerable but optimally active dose of bendamustine in combination with thalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma: Results of the MUKone trial. *Br J Haematol*. 2015;**170**(3):336–48.
100. Popat R, Brown SR, Tillotson AL, Collinson F, Flanagan LM, Williams CD, *et al.* A phase I dose-escalation study of the class 1 selective histone deacetylase inhibitor CHR-3996 in combination with tosedostat for patients with relapsed, refractory multiple myeloma: results of the muk three trial. *Blood*. 2016;**128**(Suppl. 1):3321.
101. Jenner MW, Tillotson AL, Brown SR, Flanagan LM, Sherratt D, Pawlyn C, *et al.* Velcade, Vorinostat and Dexamethasone (V2 D) in relapsed myeloma: results of the Phase 2 Muk Four Trial. *Blood*. 2015;**126**(23):1852.
102. Popat R, Brown S, Flanagan L, Hall A, Gregory W, Kishore B, *et al.*; on behalf of the Myeloma UK Early Phase Clinical Trial Network. Bortezomib, Thalidomide, Dexamethasone plus Panobinostat (VTD-P) for patients with Relapsed Multiple Myeloma: results of the MUK six phase I/II Clinical Trial. *Lancet Haematol*. 2017;**3**(12):e572–e580.
103. Popat R, Brown SR, Flanagan L, Hall A, Gregory W, Kishore B, *et al.*; on behalf of the Myeloma UK Early Phase Clinical Trial Network. Extended follow-up and the feasibility of Panobinostat maintenance for patients with Relapsed Multiple Myeloma treated with Bortezomib, Thalidomide, Dexamethasone plus Panobinostat (MUK six open label, multi-centre phase I/II Clinical Trial). *Br J Haematol*. 2018;**185**:573–8. https://doi.org/10.1111/bjh.15551
104. Croft J, Hall A, Walker K, Sherborne AL, Ellis S, Price A, *et al.* Cyclophosphamide, pomalidomide and dexamethasone significantly improves response over Poma/Dex in Relapsed/Refractory Myeloma patients previously treated with cyclophosphamide combination therapy-initial results of the randomised multicentre mukseven trial. *Blood*. 2018;**132**(Suppl. 1):3274.
105. Hinsley S, Walker K, Sherratt D, Bailey L, Reed S, Flanagan L, *et al.* The MUK eight protocol: a randomised phase II trial of Cyclophosphamide and Dexamethasone in combination with Ixazomib, in relapsed or refractory multiple myeloma (RRMM) patients who have relapsed after treatment with thalidomide, lenalidomide and a proteasome inhibitor. *Trials*. 2019;**21**:826.

