blood advances

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

Clinical Characteristics and Outcomes of IgD Myeloma: Experience across UK National Trials

Tracking no: ADV-2022-007608R1

Charles Agbuduwe (UCL Great Ormond Street Institute of Child Health, United Kingdom) Gulnaz Iqbal (University of Warwick, United Kingdom) David Cairns (University of Leeds, United Kingdom) Tom Menzies (University of Leeds, United Kingdom) Janet Dunn (University of Warwick, United Kingdom) Walter Gregory (University of Leeds, United Kingdom) Martin Kaiser (The Institute of Cancer Research, United Kingdom) Roger Owen (The Leeds Teaching Hospitals NHS Trust, United Kingdom) Charlotte Pawlyn (The Institute of Cancer Research, United Kingdom) J. Child (University of Leeds UK, United Kingdom) Faith Davies (New-York University, United States) Gareth Morgan (NYU Langone Health Care, United States) Graham Jackson (Freeman Hospital, The Newcastle Upon Tyne Hospitals NHS Foundation Trust, UK, United Kingdom) Mark Drayson (Institute of Immunology and immunotherapy, University of Birmingham, United Kingdom) Supratik Basu (University of Wolverhampton, United Kingdom)

Abstract:
IgD myeloma is a subtype often considered to have adverse features and inferior survival but there is a paucity of data from large clinical studies. We compare the clinical characteristics and outcomes of IgD myeloma patients from UK Phase III myeloma trials analysed in two groups; old (1980-2002) and recent (2002-2016) clinical trials, based on the time of adoption of novel myeloma therapies. IgD myeloma patients comprised 44/2789 (1.6%) and 70/5773 (1.2%) of the old and recent trials respectively. Overall, IgD myeloma was associated with male predominance, low-level paraproteinemia (<10g/l) and lambda light chain preference. The frequency of ultra-high risk cytogenetics was similar in IgD myeloma compared with other subtypes (4.3% vs 5.3%, p>0.99). Despite the old trial series being a younger group (median age: 59 years vs 63 years, p=0.015), there was a higher frequency of bone lesions, advanced stage at diagnosis, worse performance status and severe renal impairment compared with the recent trials. Furthermore, the early mortality rate was significantly higher for the old trial series (20% vs 4%, p=0.01). The overall response rate following induction therapy was significantly higher in the recent trials (89% vs 43%, p<0.0001) and this was consistent with improved median overall survival (48 months; 95% CI 35-67 months vs 22 months, 95% CI 16-29 months). Survival outcomes for IgD myeloma have significantly improved and are now comparable to other myeloma types due to earlier diagnosis, novel therapies and improved supportive care. (Myeloma IX International Standard Randomised Controlled Trial Number: 68454111, Myeloma XI International Standard Randomised Controlled Trial Number: 49407852)

Conflict of interest: COI declared - see note

COI notes: CA: none. GI: none. DC: Received funding from: Celgene Corporation, Amgen, Merck Sharp and Dohme - research funding. TM; Received funding from: Celgene Corporation, Amgen, Merck Sharp and Dohme - research funding. JD: none. WG: Received funding from: Celgene Corporation, Amgen, Merck Sharp and Dohme - research funding. MK: Abbvie: Consultancy; Amgen: Consultancy, Honoraria; BMS/Celgene: Consultancy, Honoraria, Research Support, Travel Support; Janssen: Consultancy, Honoraria, Travel Support; GSK: Consultancy; Karyopharm: Consultancy; Pfizer: Consultancy; Seattle Genetics: Consultancy; Takeda: Consultancy, Honoraria, Travel Support RO: none. CP: Consultancy fees, honoraria, and travel support from Amgen, Celgene Corporation, Janssen, Sanofi and Takeda Oncology. JAC: none. FD: none. GJM: Consultancy fees, honoraria, and travel support from Amgen, Celgene Corporation, Janssen, Sanofi and Takeda Oncology. GHJ: Research funding: Takeda and Celgene/BMS, Honoraria for speaking: Takeda, Celgene/BMS, Amgen, Janssen, Sanofi, Oncopeptides . MTD: Owns stock in Abbingdon Health. SB: Ad board for Sanofi, Pfizer, Bristol Myers Squibb.

Preprint server: No;

Author contributions and disclosures: CA: Writing-original draft preparation, methodology, data curation and analysis. GI: Writing- reviewing and editing, data curation for the old trials series, analysis and validation. DC: Data curation for the recent trials, writing- reviewing and editing. TM; Writing- reviewing and editing, data curation, analysis and validation of the recent trials. JD: Writing- reviewing and editing. WG: Writing- reviewing and editing. MK: Writing- reviewing and editing. RO: Writing- reviewing and editing. CP: Writing- reviewing and editing. JAC: Writing- reviewing and editing. FD: Writing- reviewing and editing. GJM: Writing- reviewing and editing, GHJ: Writing- reviewing and editing. MTD: Supervision, conceptualization, methodology, data validation, writing- reviewing and editing. SB: Supervision, conceptualization, methodology, writing- reviewing and editing.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: Email to the corresponding author

Clinical trial registration information (if any): ClinicalTrials.gov Identifier: NCT01554852. Myeloma IX: International Standard Randomised Controlled Trial Number: 68454111 Myeloma XI: International Standard Randomised Controlled Trial Number 49407852

Title	**Clinical Characteristics and Outcomes of IgD Myeloma: Experience across UK National Trials**
Running Title	**IgD Myeloma: Experience across UK National Trials**

Authors:	**Institutional affiliations:**
Charles Agbuduwe	UCL Cancer Institute and UCL Great Ormond Street Institute of Child Health, London, UK
Gulnaz Iqbal	Warwick Clinical Trials Unit, University of Warwick, Coventry, UK
David Cairns	The Clinical Trials Research Unit, University of Leeds
Tom Menzies	The Clinical Trials Research Unit, University of Leeds
Janet Dunn	Warwick Clinical Trials Unit, University of Warwick, Coventry, UK
Walter Gregory	The Clinical Trials Research Unit, University of Leeds
Martin Kaiser	The Institute of Cancer Research and The Royal Marsden Hospital, London, UK
Roger Owen	The Leeds Teaching Hospitals NHS Trust, Leeds, UK
Charlotte Pawlyn	The Institute of Cancer Research, London, UK and The Royal Marsden Hospital, London, UK
J Anthony Child	The Clinical Trials Research Unit, University of Leeds, UK
Faith Davies	Perlmutter Cancer Center, NYULangone Health, USA.
Gareth J Morgan	Perlmutter Cancer Center, NYULangone Health, USA.
Graham H Jackson	Freeman Hospital, The Newcastle Upon Tyne Hospitals NHS Foundation Trust, UK
Mark T Drayson	Institute of Immunology and immunotherapy, University of Birmingham, UK and University Hospitals Birmingham NHS Foundation Trust, UK
Supratik Basu	The Royal Wolverhampton NHS Trust, UK and University of Wolverhampton, UK

Corresponding author: Charles Agbuduwe, UCL Cancer Institute and UCL Great Ormond Street Institute of Child Health, c.agbuduwe@ucl.ac.uk.

Data sharing: Contact the corresponding author for data sharing: c.agbuduwe@ucl.ac.uk.

Abstract:

IgD myeloma is a subtype often considered to have adverse features and inferior survival but there is a paucity of data from large clinical studies. We compare the clinical characteristics and outcomes of IgD myeloma patients from UK Phase III myeloma trials analysed in two groups; old (1980-2002) and recent (2002-2016) clinical trials, based on the time of adoption of novel myeloma therapies. IgD myeloma patients comprised 44/2789 (1.6%) and 70/5773 (1.2%) of the old and recent trials respectively. Overall, IgD myeloma was associated with male predominance, low-level paraproteinemia (<10g/l) and lambda light chain preference. The frequency of ultra-high risk cytogenetics was similar in IgD myeloma compared with other subtypes (4.3% vs 5.3%, p>0.99). Despite the old trial series being a younger group (median age: 59 years vs 63 years, p=0.015), there was a higher frequency of bone lesions, advanced stage at diagnosis, worse performance status and severe renal impairment compared with the recent trials. Furthermore, the early mortality rate was significantly higher for the old trial series (20% vs 4%, p=0.01). The overall response rate following induction therapy was significantly higher in the recent trials (89% vs 43%, p<0.0001) and this was consistent with improved median overall survival (48 months; 95% CI 35-67 months vs 22 months, 95% CI 16-29 months). Survival outcomes for IgD myeloma have significantly improved and are now comparable to other myeloma types due to earlier diagnosis, novel therapies and improved

supportive care.

(Myeloma IX International Standard Randomised Controlled Trial Number: 68454111, Myeloma XI International Standard Randomised Controlled Trial Number: 49407852. ClinicalTrials.gov Identifier: NCT01554852)

Key Points:

- IgD Myeloma was historically associated with worse outcomes but we now report a standard cytogenetic risk profile and survival outcomes
- Improved IgD myeloma survival is due to earlier diagnosis, improved supportive care and response to novel anti-myeloma therapies.

INTRODUCTION

Multiple Myeloma, one of the leading causes of haematological cancer-related morbidity and mortality, is characterised by an accumulation of monoclonal plasma cells in the bone marrow and usually, a detectable monoclonal immunoglobulin (paraprotein or M-protein) in the serum.(1,2) In contrast to the more common IgG, IgA and light chain only (LCO) myeloma subtypes, the paraprotein secreted is IgD in less than 2% of cases.(3,4) IgD myeloma is biologically distinct from the common types of myeloma as it arises in a B cell prior to immunoglobulin class switching and as such may have a different clinical behaviour. IgD myeloma has been described to be associated with a relatively young age at presentation, higher incidence of extramedullary involvement, osteolytic lesions, lambda light chain predilection, renal failure and advanced disease at diagnosis.(5,6) Prior to the development of more sensitive diagnostic techniques such as immunofixation electrophoresis and the serum free light chain assay,(7) the diagnosis of IgD myeloma was more likely to be missed due to the subtle M protein spike on conventional serum electrophoresis.(8) Historically, IgD myeloma has been thought to be associated with a poor prognosis but some recent studies have suggested comparable survival rates with other subtypes.(9,10) As IgD myeloma is rare, the evidence base has been mostly limited to few small case series or other retrospective studies.

Over the past two decades, the management of myeloma has been transformed by the introduction of high-dose therapy with stem cell rescue, novel agents such as proteasome inhibitors (PIs), immunomodulatory agents (IMiDs) and monoclonal antibody therapies resulting in improved survival.(11) Furthermore, improvements in supportive care may have also contributed to better outcomes.

The aims of this study were to identify the unique features of IgD myeloma in a large series of myeloma patients and to compare outcomes between UK Medical Research Council (MRC) and National Cancer Research Institute (NCRI) myeloma clinical trials conducted before and after the introduction of novel therapies in order to determine their impact on IgD myeloma survival.

PATIENTS AND METHODS

Patient data

Myeloma patients enrolled in MRC UK Myelomatosis IV, V, VI, VIII, IX and XI clinical trials were considered for this study. For the purpose of this comparative analysis, two series were established; an "old trials" series comprising patients recruited in Myeloma IV, V, VI and VIII trials, prior to the introduction of novel myeloma therapies, and the "recent trials" series which included patients from Myeloma IX and XI. Myeloma VII trial was not included because patients were randomized to receive intensive chemotherapy and stem cell rescue.[12,13]

In the old trials conducted between 1980 and 2002, patients were randomly assigned to receive either standard dose melphalan-based chemotherapy or melphalan-based conventional dose combination chemotherapy as exemplified by doxorubicin, carmustine, cyclophosphamide, and melphalan (ABCM). Details of these trials have previously been published.(12,13)

The two most recent trials, Myeloma IX and XI, accrued trial participants from 2003 to 2016. Myeloma IX was a multicentre, randomized, open-label, phase-III, and factorial-design clinical trial conducted in the UK (International Standard Randomised Controlled Trial Number: 68454111). The trial protocol details for Myeloma IX have been published previously.(14,15) In summary, newly-diagnosed patients aged 18 years or older with symptomatic multiple myeloma were allocated to either an intensive or non-intensive pathway. Details of the randomisation strategy and treatment arms are summarised in supplementary figures S1a and S1b. For the intensive pathway, Oral cyclophosphamide, thalidomide, and dexamethasone (CTD) was compared with infusional cyclophosphamide,

vincristine, doxorubicin, and dexamethasone (CVAD) in patients with newly diagnosed multiple myeloma. For the non-intensive pathway, patients were randomised to either melphalan plus prednisolone (MP) or CTDa (CTD with a reduced dose of dexamethasone and lower starting dose of thalidomide). The exclusion criteria included pregnancy, asymptomatic myeloma, solitary bone or extramedullary plasmacytoma, previous or concurrent active malignancies, and presence of severe acute kidney injury (AKI) unresponsive to up to 72 hours of rehydration, characterised by a serum or plasma creatinine >500 μmol/L, a urine output less than 400ml/day, or a requirement for dialysis.

The Myeloma XI trial (International Standard Randomised Controlled Trial Number 49407852) was a phase III, randomised, multi-centre, parallel group design, open-label trial comparing thalidomide, lenalidomide, carfilzomib and bortezomib combinations and of lenalidomide (+/- vorinostat) as maintenance treatment in newly diagnosed symptomatic myeloma patients 18 years and older.(16,17) A summary of the randomisation and treatment arms are shown in supplementary figures S2a and S2b. The exclusion criteria were similar to those for the Myeloma IX trial.

Baseline clinical and biochemical characteristics were recorded for all patients at enrolment. Serum creatinine, β-2 microglobulin (Sβ2m), paraprotein type and levels, and urine creatinine and light chain levels were measured by a central laboratory in Birmingham, United Kingdom. Participating centres provided clinical details, information on skeletal disease–related events, full blood count (FBC), serum albumin and urea, and plasma cell infiltration of bone marrow. Translocations t(4;14), t(14;16) and t(14;20) together with the copy number abnormalities del(17p), gain/amp(1q) have all been associated with adverse outcomes and the presence of more than one adverse lesion is associated with even worse

prognosis. (18–20) Three cytogenetic risk groups were defined based on the number of adverse cytogenetic abnormalities identified at recruitment: ultra-high risk (2 or more), high risk (one) and standard risk (none). Disease response and progression were defined according to trial protocol criteria and a final report to ascertain the cause of death and a summary of the clinical course was recorded in the event of a death.

All trial protocols were approved by a multicentre research ethics committee as well as the relevant local ethics committees and institutional review boards. All patients gave written informed consent in accordance with the Declaration of Helsinki.

Differences in patient characteristics by paraprotein group were investigated using Pearson's Chi-squared or Fisher's exact tests. Overall survival was defined as the time between date of entry to either date of death or date last seen. Survival curves were constructed using the Kaplan-Meier method and the log-rank test was used to assess differences between paraprotein class groups. The progression-free interval was calculated from date of recruitment to either the date of progression or censored at the date of death in patients who died progression-free or censored at the date last seen for patients alive without progression. The date of data cut off was 26 November 2021. Statistical analyses of the MRC trials were performed using SAS statistical software (SAS Institute, SAS Circle, Cary, North Carolina, USA). The visual abstract was created with BioRender.com.

RESULTS

Baseline patient characteristics

Forty-four (44) IgD myeloma patients were identified from the older Myeloma trials accounting for approximately 2% of the 2789 total myeloma cases with an identifiable paraprotein (supplementary table S1.1). The commonest paraprotein type was IgG (56%) followed by IgA (26%) and LCO (12%). The median age of IgD myeloma patients was 59 years (Figure 1) and 20% were 65 years or older at the time of diagnosis (Table 1). In this series, most IgD Myeloma patients (61%) had a performance status of 3 or more and this was comparable to light chain only myeloma (60%). IgD and LCO myeloma were also similar in rates of elevated serum β2-microglobulin levels. Significant renal impairment, as indicated by elevated serum creatinine and urea, were highest in LCO and IgD myeloma but more marked for the former (supplementary table S1.2). Severe anaemia (<7.5g/dL) was most frequently observed in IgD myeloma patients perhaps reflecting higher bone marrow involvement as half of these patients had bone marrow plasma cells greater than 50%. Hypercalcaemia was more common in IgA myeloma (45%). There were however fewer lytic bone lesions in IgA myeloma compared with IgD and LCO myeloma which had the highest rates (supplementary table S1.2). There was no significant difference in bone pain and fractures across all groups.

Seventy (70) IgD myeloma patients were recruited into the recent trials accounting for 1.2% of the 5773 total. As observed in the old trials, rates of severe renal impairment were higher in IgD and LCO myeloma subgroups in the recent trials (Figure 1, supplementary tables 1.2 and 1.3) but this was considerably less when compared with the old trials. Both IgD myeloma series were similar in lambda light chain preference, higher male prevalence and

low-level paraproteinaemia but the old trials series had significantly worse performance status, advanced ISS stage, higher serum β2-microglobulin levels, severe renal impairment and more frequent lytic lesions at diagnosis despite the recent trial series being older (median age 59 vs 63 years, p=0.015) [Table 1 and Figure 1]. In the recent trials, 73% of IgD myeloma patients were allocated to the intensive arms.

IgD Myeloma patients in the recent trials had a similar distribution of the cytogenetic risk groups compared with other myeloma subtypes (Figure 2A) with 3 (4.3%) of these patients identified as ultrahigh risk at diagnosis. There was an overrepresentation of ultrahigh risk cytogenetics in the IgA myeloma group compared with the other subtypes (8.4% vs 5.3%, p<0.0001) (Supplementary Table S2). The t(11;14) chromosomal rearrangement was assessed at diagnosis in 28 IgD myeloma patients and this cytogenetic abnormality was present in 6 (21%) compared with 95 (11%) of 838 IgG and 207 (15%) of 1339 non-IgD myeloma patients (Supplementary tables S5 and S6).

Clinical responses post-induction therapy

Comparison of induction response rates among IgD myeloma patients between the old and recent clinical trial series showed significant improvements in overall response rates (43% vs 89% p<0.0001), (Figure 2B). There was a similar trend towards deeper remissions in the IgD myeloma participants in the recent trials; Complete Response (CR) rate (40% vs 27% p=0.23) (supplementary table S4).

Survival outcomes

In the old trials, IgD myeloma patients had the shortest median overall survival of 22 months (95% confidence interval: 16-29 months) and this was similar for LCO myeloma

(median 23 months, confidence interval 18-27 months) (Figure 3A). The longest median overall survival was observed in IgG myeloma patients (median: 31 months, 95% confidence interval: 29 - 33 months) while that for IgA myeloma was 28 months (95% confidence interval: 26 – 31 months). Similarly, the median progression-free survival was longest for IgG Myeloma (21 months, 95% CI 20 – 22) and shortest for IgD Myeloma (16 months, 95% CI 13 – 20) ($p<0.0001$)(Figure 3B). A significantly higher early death rate, within 100 days of trial entry, was observed for IgD myeloma patients compared with IgG/IgA (20% versus 14% respectively, $p<0.001$).

In the pooled analysis of the recent trials, the median overall survival for IgD myeloma was 48 months (95% CI: 35-67 months) compared with 61 months (95% CI: 59-63 months) for the other subtypes combined (Figure 4A). This difference was not statistically significant ($p=0.466$, HR 0.89, 95% confidence interval 0.66-1.21). There was also no significant difference in median progression-free survival (PFS) between IgD myeloma and other subtypes; 23 months vs 22 months respectively ($p=0.522$, HR 1.09, 95% CI 0.84-1.42) (Figure 4B). Direct comparison of overall survival between specific myeloma subtypes showed that IgG and LCO myeloma had the longest median overall survival (Figure 4C), 64 months (95% CI 62-67 months) and 62 months (95% CI 55-70 months) respectively. The median overall survival for IgA myeloma was 51 months (95% CI 48-54 months). Progression-free survival was similar for all patients irrespective of paraprotein type (Figure 4D).

To evaluate the influence of cytogenetics on survival, a stratified analysis was performed for the recent trials series. The frequency of standard, high and ultra-high risk cytogenetics groups were similar between IgD and IgG myeloma but the frequency of ultra-high risk cytogenetics was higher for IgA myeloma compared with IgG (8.4% vs 4.5%, $p<0.0001$)

(Supplementary table S2). The median overall and progression-free survival for IgD myeloma was comparable with those of other subtypes within each of the three cytogenetic risk groups (Supplementary Figures 3a and 3b). The median overall survival values for IgD myeloma subcategories were 57 months (95% CI 15 - not evaluable), 53 months (95% CI 28-80) and 28 months (95% CI 17-48) respectively for standard, high and ultra-high cytogenetic risk groups (Figure 4E). The median progression-free survival was shortest in the ultra high-risk group; 16 months (95% CI 10-26) and longest in the high-risk group; 24 months (95% CI 12-37) (Figure 4F).

Mortality data

At the time of data cut-off, 44 and 43 deaths had been recorded among IgD Myeloma participants in the old and recent trial respectively (Table 2) with disease progression being the main cause of mortality in both groups. A significantly higher rate of early mortality, within 100 days of trial entry, was observed in the old trials IgD myeloma group (20% vs 4%, p=0.01). Similar rates of deaths due to renal failure and cardio-respiratory disease were observed between the two groups. Interestingly, infection was more commonly recorded as the cause of death in the recent trial series (2% vs 19%, p=0.01).

DISCUSSION

Given the rarity of IgD myeloma, there are only few published studies on the clinical characteristics and outcomes of the disease. This study reports the largest set of IgD myeloma patients from randomised clinical trials. Most previously published IgD myeloma studies have been retrospective case series, registry data or single-centre reports and some of these are summarised in Table 3. One of the strengths of this study is the fact that the

diagnostic and follow up laboratory samples were analysed in a central laboratory, thus permitting direct comparability between the patient groups in our study.

Previous studies have reported associations of IgD myeloma with male sex, younger age at diagnosis, hypercalcaemia, higher serum β_2-microglobulin and creatinine, lambda light chain predilection, amyloidosis and a greater degree of bone involvement.(21–24) Some associations such as higher frequency of male patients, younger median age and lambda light chain predilection were also observed in this study. However, despite being an older group, IgD myeloma patients in the recent trials had less renal impairment and hypercalcaemia, better performance status and earlier ISS stage at diagnosis compared with the old trials group. The most plausible explanation for this observation would be earlier diagnosis permitted by the introduction of sensitive diagnostic techniques such as the serum free light chain assay. Interestingly, we also found striking similarities in baseline characteristics between IgD and LCO myeloma, possibly reflecting the diagnostic challenge posed by the lack of a characteristic monoclonal protein spike on conventional electrophoresis for both myeloma subtypes. Possibly due to the difficulty with establishing the diagnosis of IgD myeloma prior to the introduction of more sensitive diagnostic methods such as the Serum-free light chain assay, patients were at an advanced stage with a higher disease burden as observed in the old trials. Consequently, the lesser degree of severe renal impairment observed in the recent trials compared with the older trials may also reflect the improved management of renal complications. The most striking evidence for this can be seen in the marked improvement in the median overall survival of LCO myeloma between the two series (23 months *vs* 62 months). A recently published analysis of outcomes of Myeloma XI trial patients by baseline renal function showed that severe renal impairment

was associated with inferior survival and recovery of renal function post-induction treatment was associated with younger age (<70 years), a higher baseline free light chain level >1000 mg/L, and/or a free light chain response of >90%.(17) Therefore, the improved renal profiles of the recent trials group would have made a significant contribution to the improvements in survival outcomes of IgD myeloma patients.

Despite the IgD patients in the old trials series being younger, this group had a worse baseline performance status and ISS stage, correlating with inferior survival outcomes for this group. Comparison of overall survival for IgD myeloma across the trials indicates a significant improvement in median survival from 22 months (95% CI: 16-29 months) for the old trials series to 48 months (95% CI: 35-67 months) in the recent trials. A similar improvement in progression-free survival was observed (16 months, 95% CI 13 – 20 *vs* 23 months, 16 - 29). As the recent trials were conducted in the era of IMiDs and PIs, it is likely that the improvement in outcomes, particularly the PFS, is attributable to these novel therapies. Interestingly, of all the myeloma subtypes, IgD myeloma has seen the largest improvement in PFS between the two series. A similar improvement in IgD myeloma survival has been reported by the Greek Myeloma Study Group for patients treated from 2000-2012 compared with those treated before 2000 (44 months vs 51.5 months, p= 0.018), the time point when the first IMiD became available.(9) Furthermore, a consistent improvement in median overall survival is apparent from published IgD myeloma studies over the years (Table 3). One of the earliest case series of IgD myeloma in Japanese patients published in 1991(25), well before the introduction of novel anti-myeloma agents, reported a median overall survival of 12 months in contrast to a recently published multicentre retrospective Asian Myeloma Network (AMN) study involving IgD myeloma patients from

China, Korea and Singapore which reported a median overall survival of 36.5 months for the entire IgD myeloma cohort.(26) There was an unusually high prevalence of IgD myeloma (2 - 8.8%) in the study population with a higher frequency of t(11;14) chromosomal rearrangement in the IgD myeloma cohort compared with other myeloma subtypes (24.7% of IgD MM *vs* 13.5% of non-IgD MM). Similarly in our recent trials series, the frequency of t(11;14) in IgD myeloma was approximately twice that of the IgG subtype. This increased frequency of t(11;14) in IgD myeloma warrants further study due to the therapeutic potential of BCL-2 inhibitors in this group of patients.

Furthermore, IgD myeloma was not associated with a higher rate of adverse cytogenetics compared with other subtypes however, we observed an increased frequency of the ultrahigh risk cytogenetic profile in IgA myeloma, correlating with a relatively shorter OS compared with IgG myeloma (Figure 4C). Other studies have similarly reported higher frequencies of adverse risk cytogenetics such as t(4;14) in IgA myeloma patients with resulting poorer outcomes compared with IgG myeloma.(27–29) Furthermore, the significant difference in median OS between IgG and IgA myeloma in our study is not seen within the ultra-high risk cytogenetics subgroup which has a uniformly inferior outcome (IgA 33 months, 95% CI: 26-40 vs IgG 29 months, 95% CI: 22-36) (supplementary figure S4). These observations support the use of cytogenetic risk stratification rather than paraprotein type in assigning prognostic categories in myeloma.

The impact of novel therapies on the outcomes of IgD myeloma could also be deduced from the clinical response rates between the old and recent trial series as the overall response rate was significantly higher in the recent trials (89% vs 43%, $p<0.0001$) with a trend

towards deeper remissions (CR and VGPR). In a study conducted in the pre-novel therapy era, Morris et al previously reported significantly higher Complete Response (CR) rate in IgD Myeloma patients compared with the more common myelomas (43.8% vs 23.2%) but an inferior Overall Survival (OS) (43.5 months vs 63.2 months, p< 0.0001) suggesting a high relapse rate in this patient group.(22) Similar findings were reported in a smaller study of 77 myeloma patients undergoing Autologous Stem cell Transplant (ASCT) in Korea; despite significantly higher complete response rates post-ASCT, (75% vs 58%), IgD Myeloma patients had much worse event-free (6.9 months vs 11.5 months, p=0.01) and overall survival (12 months vs 55.5 months, p<0.01) when compared to other myeloma subtypes.(30) It is noteworthy that the majority of patients in this study received conventional chemotherapy regimens as opposed to novel agents. Given the improvements in IgD progression-free survival in our recent trial series, it is possible to conclude that novel agents have improved both the depth and duration of clinical responses in IgD myeloma patients.

In the current study, the most frequent cause of death for both IgD myeloma series was disease progression with a significantly higher rate of early mortality in the old trials which is likely due to a combination of factors notably severe renal impairment and advanced disease stage. An explanation for the higher rate of infections reported as a cause of death in the recent trials series is likely a result of longer survival as well as the impact of multiple lines of therapy.

One of the limitations of this study has been the relatively limited number of IgD myeloma patients which made comparison with the other more common myeloma subtypes statistically challenging. Furthermore, cytogenetics results were not available for the old trials for comparison with the available data from the recent trials. The exclusion of patients with end-stage renal impairment from the clinical trials limits the extrapolation of the

findings to this population but as the comparison of outcomes was between two clinical trial series with similar inclusion and exclusion criteria, apart from the age limit of 75 years for the older trials, the observed differences in outcomes are not likely to be attributable to selection bias. Furthermore, the central analysis of the OPTIMAL and MERIT trials of newly diagnosed Myeloma patients in the UK presenting with severe renal impairment reported comparable proportions of IgD myeloma indicating that significant IgD myeloma patients were not being missed by exclusion of end stage renal failure patients from the clinical trials analysed in this publication.(31)

To our knowledge, this is the first study specifically reporting the characteristics and outcomes of IgD Myeloma from large Phase III randomised clinical trials. Our data suggests that with improved diagnostic tests permitting earlier diagnosis and the introduction of novel anti-myeloma agents, overall and progression-free survival of IgD myeloma is now comparable to other myeloma subtypes. We argue that the historical association of IgD myeloma with a dismal prognosis was largely due to renal impairment and advanced stage possibly linked to delays in establishing the diagnosis. Our data also underlines the importance of cytogenetic risk stratification as patients with adverse cytogenetic profiles had poorer outcomes irrespective of the myeloma subtype and that IgD myeloma was not associated with a higher rate of adverse cytogenetics. Therefore, in the era of novel myeloma therapies, cytogenetic risk stratification is of greater prognostic value than paraprotein type.

Acknowledgements:

The authors appreciate all the clinical trial investigators across the participating hospitals in the UK and particularly the trial participants.

Authorship

Contribution: CA: Writing-original draft preparation, methodology, data curation and analysis. GI: Writing- reviewing and editing, data curation for the old trials series, analysis and validation. DC: Data curation for the recent trials, writing- reviewing and editing. TM; Writing- reviewing and editing, data curation, analysis and validation of the recent trials. JD: Writing- reviewing and editing. WG: Writing- reviewing and editing. MK: Writing- reviewing and editing. RO: Writing- reviewing and editing. CP: Writing- reviewing and editing. JAC: Writing- reviewing and editing. FD: Writing- reviewing and editing. GJM: Writing- reviewing and editing, GHJ: Writing- reviewing and editing. MTD: Supervision, conceptualization, methodology, data validation, writing- reviewing and editing. SB: Supervision, conceptualization, methodology, writing- reviewing and editing.

Conflict-of-interest statement: DC: Received funding from: Celgene Corporation, Amgen, Merck Sharp and Dohme - research funding. TM; Received funding from: Celgene Corporation, Amgen, Merck Sharp and Dohme - research funding. WG: Received funding from: Celgene Corporation, Amgen, Merck Sharp and Dohme - research funding. MK: Abbvie: Consultancy; Amgen: Consultancy, Honoraria; BMS/Celgene: Consultancy, Honoraria, Research Support, Travel Support; Janssen: Consultancy, Honoraria, Travel Support; GSK: Consultancy; Karyopharm: Consultancy; Pfizer: Consultancy; Seattle Genetics: Consultancy; Takeda: Consultancy, Honoraria, Travel Support CP: Consultancy fees, honoraria, and travel support from Amgen, Celgene Corporation, Janssen, Sanofi and Takeda Oncology. GJM: Consultancy fees, honoraria, and travel support from Amgen, Celgene Corporation, Janssen, Sanofi and Takeda Oncology. GHJ: Research funding: Takeda and Celgene/BMS, Honoraria for speaking: Takeda, Celgene/BMS, Amgen, Janssen, Sanofi, Oncopeptides . MTD: Owns stock in Abbingdon Health. SB: Ad board for Sanofi, Pfizer, Bristol Myers Squibb. The remaining authors declare no conflict of interest.

REFERENCES

1. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014 Nov 1;15(12):e538-48.

2. C J van de Donk NW, Pawlyn C, Yong KL. Seminar Multiple myeloma. Vol. 397, The Lancet. 2021.

3. Morris C, Iacobelli S, Gahrton G, Biezen A van, Drake M, Garderet L, et al. Efficacy and Outcome of Allogeneic Transplantation in IgD and Nonsecretory Myeloma. A Report on Behalf of the Myeloma Subcommittee of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation. Biology of Blood and Marrow Transplant. 2010;21(6):1054–8.

4. Wechalekar A, Amato D, Chen C, Keith Stewart A, Reece D. IgD multiple myeloma?a clinical profile and outcome with chemotherapy and autologous stem cell transplantation. Annals of Hematology. 2005 Feb 22;84(2):115–7.

5. Djidjik R, Lounici Y, Chergeulaïne K, Berkouk Y, Mouhoub S, Chaib S, et al. IgD multiple myeloma: Clinical, biological features and prognostic value of the serum free light chain assay. Pathologie Biologie. 2015 Sep 1;63(4–5):210–4.

6. Hobbs JR, Corbett AA. Younger Age of Presentation and Extraosseous Tumour in IgD Myelomatosis. 1969;

7. Drayson M, Tang LX, Drew R, Mead GP, Carr-Smith H, Bradwell AR. Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. Blood [Internet]. 2001 May 1 [cited 2021 Nov 4];97(9):2900–2. Available from: http://ashpublications.org/blood/article-pdf/97/9/2900/1673621/h8090102900.pdf

8. Djidjik R, Lounici Y, Chergeulaïne K, Berkouk Y, Mouhoub S, Chaib S, et al. IgD multiple myeloma: Clinical, biological features and prognostic value of the serum free light chain assay. Pathologie Biologie. 2015;63(4):210–4.

9. Zagouri F, Kastritis E, Symeonidis AS, Giannakoulas N, Katodritou E, Delimpasi S, et al. Immunoglobulin D myeloma: clinical features and outcome in the era of novel agents. European Journal of Haematology. 2014 Apr 1;92(4):308–12.

10. Chen L, Fan F, Deng J, Xu J, Xu A, Sun C, et al. Clinical characteristics and prognosis of immunoglobulin D myeloma in the novel agent era. Annals of Hematology. 2019 Apr 5;98(4):963–70.

11. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008 Mar 1;111(5):2516–20.

12. Drayson M, Begum G, Basu S, Makkuni S, Dunn J, Barth N, et al. Effects of paraprotein heavy and light chain types and free light chain load on survival in myeloma: an analysis of patients receiving conventional-dose chemotherapy in Medical Research Council UK multiple myeloma trials. Blood. 2006 Sep 15;108(6):2013–9.

13. Augustson BM, Begum G, Dunn JA, Barth NJ, Davies F, Morgan G, et al. 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. Journal of Clinical Oncology. 2005 Dec 20;23(36):9219–26.

14. Morgan GJ, Davies FE, Gregory WM, Bell SE, Szubert AJ, Navarro Coy N, et al. Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results. Haematologica. 2012 Mar;97(3):442–50.

15. 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 Aug 4;118(5):1231–8.

16. 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. The Lancet Oncology. 2019 Jan 1;20(1):57–73.

17. Rana R, Cockwell P, Drayson M, Cook M, Pratt G, Cairns DA, et al. Renal outcome in patients with newly diagnosed multiple myeloma: Results from the UK NCRI Myeloma XI trial. Blood Advances. 2020 Nov 24;4(22):5836–45.

18. Boyd KD, Ross FM, Chiecchio L, Dagrada GP, Konn ZJ, Tapper WJ, et al. A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: Analysis of patients treated in the MRC Myeloma IX trial. Leukemia. 2012 Feb;26(2):349–55.

19. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised international staging system for multiple myeloma: A report from international myeloma working group. Journal of Clinical Oncology. 2015;33(26):2863–9.

20. 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. 2018 Jan 1;32(1):102–10.

21. Jancelewicz Z, Takatsuki K, Sugai S, Pruzanski W, Rowe DS FJ, Fahey JL et al, et al. IgD Multiple Myeloma. Archives of Internal Medicine. 1975 Jan 1;135(1):87.

22. Morris C, Drake M, Apperley J, Iacobelli S, van Biezen A, Bjorkstrand B, et al. Efficacy and outcome of autologous transplantation in rare myelomas. Haematologica [Internet]. 2010 Dec [cited 2016 Jul 18];95(12):2126–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20971818

23. Bladé J, Lust JA, Kyle RA. Immunoglobulin D multiple myeloma: Presenting features, response to therapy, and survival in a series of 53 cases. Journal of Clinical Oncology. 1994 Sep 21;12(11):2398–404.

24. Kim MK, Suh C, Lee DH, Min CK, Kim SJ, Kim K, et al. Immunoglobulin D multiple myeloma: response to therapy, survival, and prognostic factors in 75 patients. Annals of Oncology . 2010 Aug 2;

25. Shimamoto Y, Anami Y, Yamaguchi M. A new risk grouping for IgD myeloma based on analysis of 165 Japanese patients. European Journal of Haematology [Internet]. 1991 Oct 1 [cited 2021 Dec 10];47(4):262–7. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-0609.1991.tb01569.x

26. Liu J, Hu X, Jia Y, Lu J, Lee JH, Kim K, et al. Clinical features and survival outcomes in IgD myeloma: a study by Asia Myeloma Network (AMN) [Internet]. Leukemia. Springer Nature; 2020 [cited 2021 Feb 26]. p. 1–6. Available from: https://doi.org/10.1038/s41375-020-01060-w

27. Yadav P, Merz M, Mai EK, Försti A, Jauch A, Goldschmidt H, et al. Cytogenetic aberrations in multiple myeloma are associated with shifts in serum immunoglobulin isotypes distribution and levels. Vol. 103, Haematologica. Ferrata Storti Foundation; 2018. p. e162–4.

28. Usmani SZ, Hoering A, Cavo M, Miguel JS, Goldschimdt H, Hajek R, et al. Clinical predictors of long-term survival in newly diagnosed transplant eligible multiple myeloma — an IMWG Research Project. Blood Cancer Journal. 2018 Dec 23;8(12):123.

29. Chang H, Sloan S, Li D, Zhuang L, Yi QL, Chen CI, et al. The t(4;14) is associated with poor prognosis in myeloma patients undergoing autologous stem cell transplant. British Journal of Haematology. 2004 Apr 1;125(1):64–8.

30. Kim MK, Suh C, Lee DH, Min CK, Kim SJ, Kim K, et al. Immunoglobulin D multiple myeloma: response to therapy, survival, and prognostic factors in 75 patients. Ann Oncol [Internet]. 2011 Feb 1 [cited 2021 Dec 10];22(2):411–6. Available from: https://pubmed.ncbi.nlm.nih.gov/20682550/

31. Drayson M, Behrens J, Cohen D, Iggo N, Gregory W, Bell S, et al. A351 Serum FLC Levels Can Be Reduced Rapidly; Lower Levels Are Associated with Renal Recovery. Clinical Lymphoma and Myeloma. 2009 Feb;9:S57–8.

Figure 1. Comparison of baseline patient characteristics for the myeloma subsets across UK MRC/NCRI clinical trials.

Plt, platelet count. Hb, Haemoglobin concentration. PS, Performance Status. LCO, Light Chain Only Myeloma.

The box and whisker plot compares the ages of IgD myeloma patients in the respective trials. Box indicates median and interquartile range, whiskers indicate range.

Figure 2.

Figure 2A: (Top) Cytogenetic risk stratification of participants in the recent UK myeloma clinical trials (Myeloma IX and XI). Graph shows the percentage of the cytogenetic risk groups for the various myeloma subtypes.

(Bottom) Comparison proportions of the cytogenetic risk groups for IgD myeloma *versus* other myeloma subtypes.

UHiR, Ultra High risk; HiR, High risk; SR, Standard risk; N/A, not available.

Figure 2B: Clinical responses following induction therapy based on the International Myeloma Working Group (IMWG) response criteria.

CR, Complete Response; VGPR, Very Good Partial Response; PR, Partial response; SD; Stable disease; PD, Persistent disease, N/A, Not Available.

Figure 3. Old Myeloma trials:

A: Overall Survival of myeloma patients stratified by paraprotein type.

B: Progression-free survival of myeloma patients stratified by paraprotein type.

Figure 4. Recent Myeloma trials:

A. Kaplan-Meier plot comparing overall survival between IgD Myeloma *versus* other subtypes.
B. Kaplan-Meier plot comparing progression-free survival between IgD Myeloma *versus* other subtypes.
C. Kaplan-Meier plot of Overall survival stratified by paraprotein class.
D. Kaplan-Meier plot of progression-free survival stratified by paraprotein class.
E. Overall survival of IgD Myeloma patients stratified by cytogenetic risk group
F. Progression-free survival of IgD myeloma patients stratified by cytogenetic risk group

OS, Overall survival. PFS, progression-free survival.

TABLES

		Old Trials (MM IV, V VI & VIII) N=44	Recent trials (MM IX & MM XI) N=70	p value
Characteristic	**Grouping**	**n (%)**	**n (%)**	
Age	**<=65 years**	**35 (80)**	**38 (54)**	0.0088
	>65 years	**9 (20)**	**32 (46)**	
Sex	***Male***	**31 (70)**	**48 (69)**	0.99
	Female	**13 (30)**	**22 (31)**	
Serum creatinine (µmol/l)	***<130***	**22 (50)**	**48 (68)**	0.04
	130-200	**6 (14)**	**11 (16)**	
	>200	**16 (36)**	**11 (16)**	
	missing	**0 (0)**	**0 (0)**	
Serum □2 Microglobulin (mg/l)	***<3.5***	**3 (7)**	**16 (23)**	0.0044
	3.5-5.5	**7 (16)**	**15 (21)**	
	>5.5	**33 (75)**	**30 (43)**	
	missing	**1 (2)**	**9 (13)**	
ISS Stage	***Stage I***	**2 (4.5)**	**15 (21)**	0.0045
	Stage II	**7 (16)**	**15 (21)**	
	Stage III	**33 (75)**	**30 (43)**	
	missing	**2 (4.5)**	**10 (14)**	
Performance status	***0-2***	**15 (34)**	**64 (91)**	<0.0001
	3-4	**27 (61)**	**4 (6)**	
	missing	**2 (5)**	**2 (3)**	
Lytic lesions	*Present*	**34 (77)**	**37 (53)**	0.03
	Absent	**7 (16)**	**21 (30)**	
	Not known/missing	**3 (7)**	**12 (17)**	
Serum calcium	*≤2.6*	**20 (45)**	**54 (77)**	<0.0001

(mmol/l)	*>2.6*	**10 (23)**	**16 (23)**	
	missing	**14 (32)**	**0 (0)**	
Haemoglobin (g/l)	*<100*	**20 (45)**	**39 (56)**	0.07
	=>100	**21 (48)**	**31 (44)**	
	missing	**3 (7)**	**0 (0)**	
Platelet count (x10^9/L)	*<150*	**10 (23)**	**7 (10)**	0.0016
	≥150	**29 (66)**	**63 (90)**	
	missing	**5 (11)**	**0 (0)**	
IgD Serum Paraprotein quantification (g/l)	*<10*	**24 (55)**	**36 (51)**	0.9338
	=>10	**14 (32)**	**23 (33)**	
	missing	**6 (13)**	**11 (16)**	
Light chain type	*Lambda*	**29 (66)**	**43 (61)**	0.3944
	Kappa	**14 (32)**	**21 (30)**	
	missing	**1 (2)**	**6 (9)**	
Bone marrow Plasma cell (%)	*<20*	**6 (14)**	**11 (16)**	0.26
	20-50	**9 (20)**	**25 (36)**	
	>50	**15 (34)**	**20 (28)**	
	missing	**14 (32)**	**14 (20)**	

Table 1. Baseline IgD myeloma patient characteristics

IgD Myeloma deaths	Old Trials (n=44) n (%)	Recent trials (n=70) n (%)	p
All deaths	44 (100)	43 (61)	
Progressive disease	21 (48)	21 (49)	0.99
Infection	1 (2)	8 (19)	0.01
Renal failure	3 (7)	4 (9)	0.7
Cardiac/respiratory disease	5 (11)	3 (7)	0.7
Malignancy other than myeloma	1 (2)	1 (2)	0.99
Other causes	13 (29)	6 (14)	0.12
Early mortality (all causes within 100 days of trial entry)	9 (20)	3 (4)	0.01

Table 2. Causes of IgD myeloma deaths in MRC/UKRI Myeloma clinical trials

Study	Study population	Median age (years)	Male (%)	Hb <100 g/l (%)	Serum creatinine >2mg/dl (%)	Extramedullary Involvement (%)	Lambda light chain association (%)	Median overall survival (months)
Jancelewicz et al 1975	Retrospective review of IgD myeloma cases (n=133)	56	76	61	31	73	90	9
Shimamoto et al 1991	Retrospective study of Japanese patients with IgD myeloma (n=165)	56	76	50 (Hb<85 g/L)	43	27	82	12
Blade et al 1994	Single US centre report of IgD myeloma cases diagnosed 1965-1992 (n=53)	60	62	29	33	19	60	21
Morris et al 2010	Retrospective study of IgD myeloma cases in the EBMT myeloma database for patients undergoing autologous stem cell transplants 1986-2007 (n=379)	54	65	~50	Median 130mmol/l (1.47mg/dl)	-	75	43.5
Kim et al 2011	Korean myeloma registry database 1997-2009 (n=77)	57	67	75	53	11	89	18.5
Zagouri et al 2013	Cohort study by the Greek Myeloma Study group 2000-2012 (n=31)	65	52	58	52	-	84	51.5
Liu et al 2020	Asian Myeloma Network (China, Korea and Singapore) multicentre cohort study 2012-2019 (n=356)	56	68	65	36	19	89	36.5

Table 3: Comparison of clinical characteristics and median overall survival of IgD myeloma patients between major published studies.

EBMT- European Society for Blood and Bone Marrow Transplantation, US-United States, Hb-haemoglobin.

Figure 1

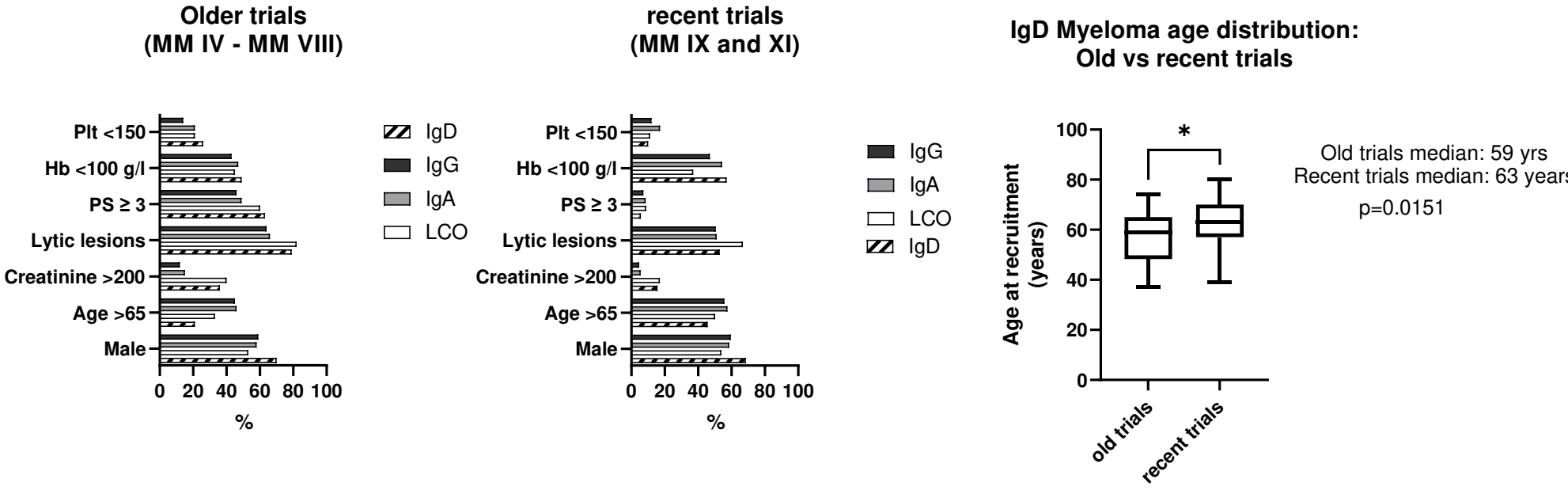


Figure 2

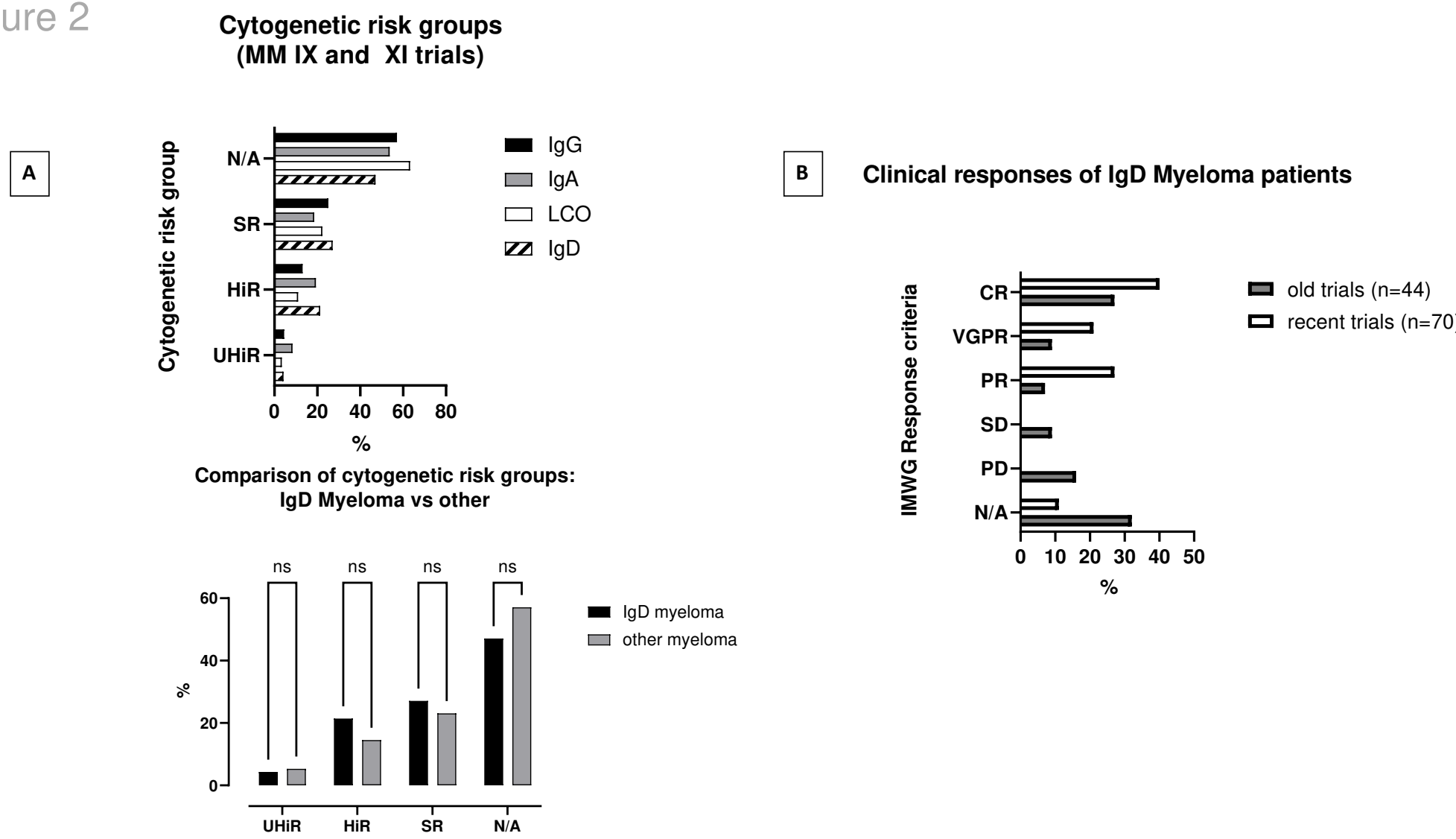
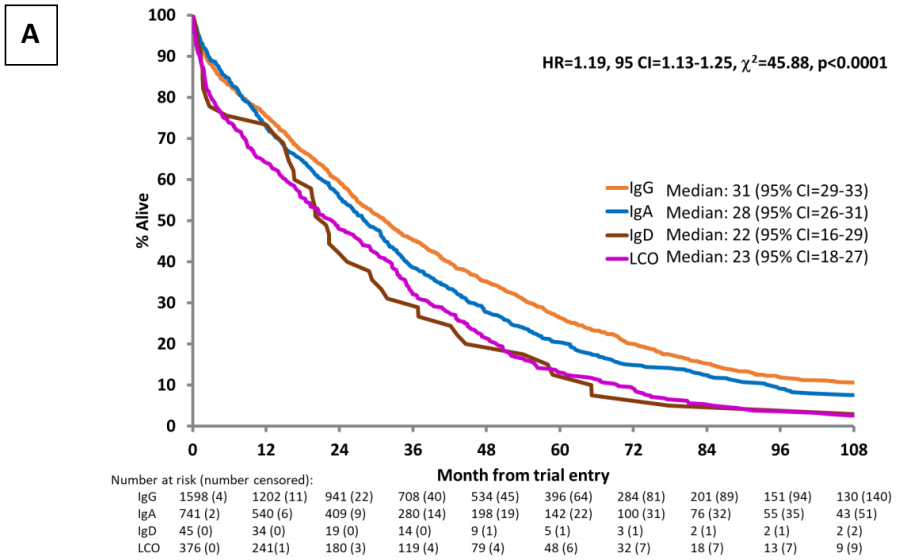


Figure 3



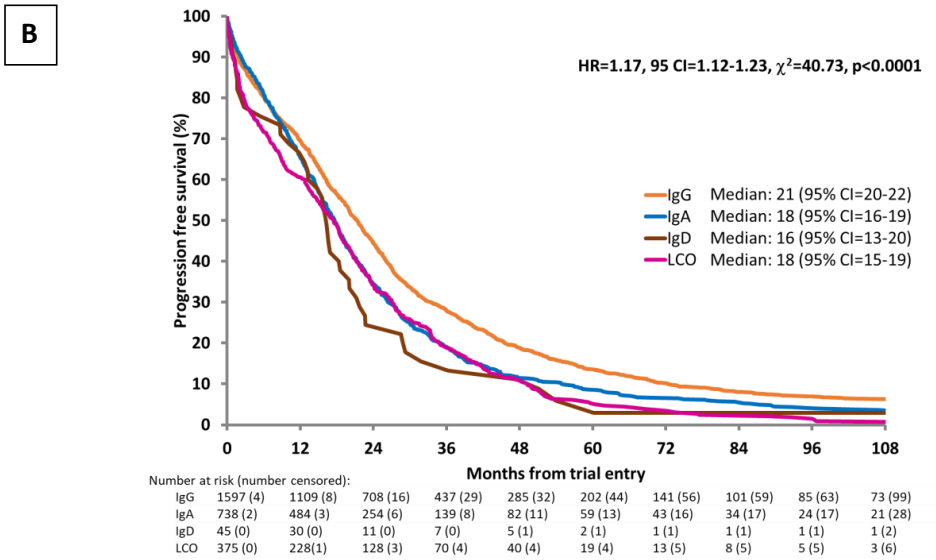
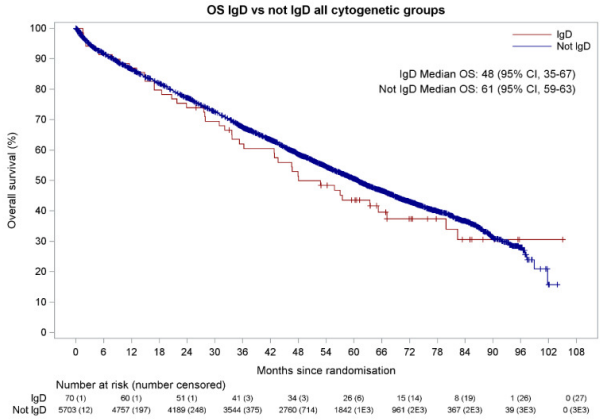
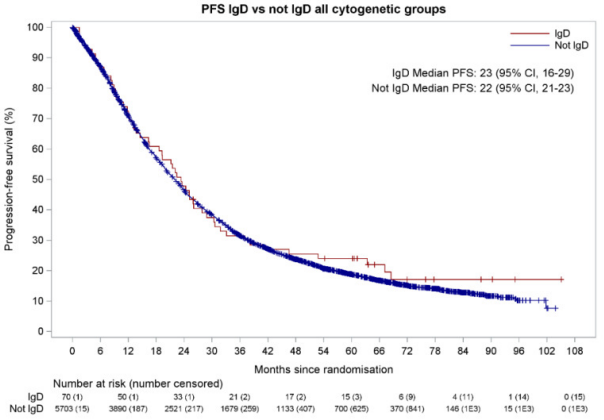


Figure 4

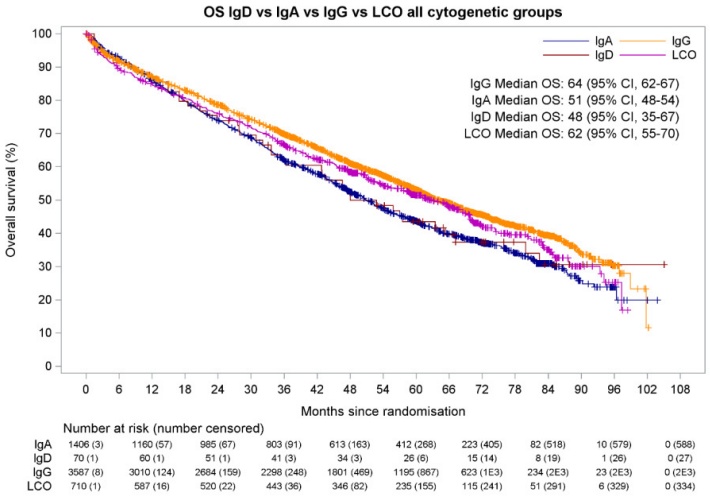
A



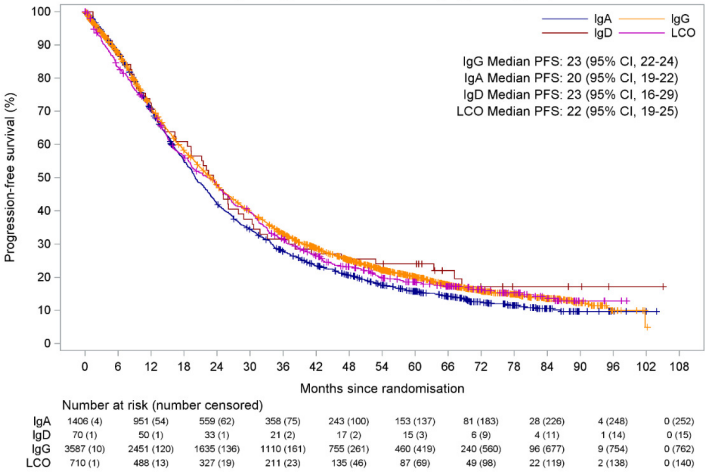
B



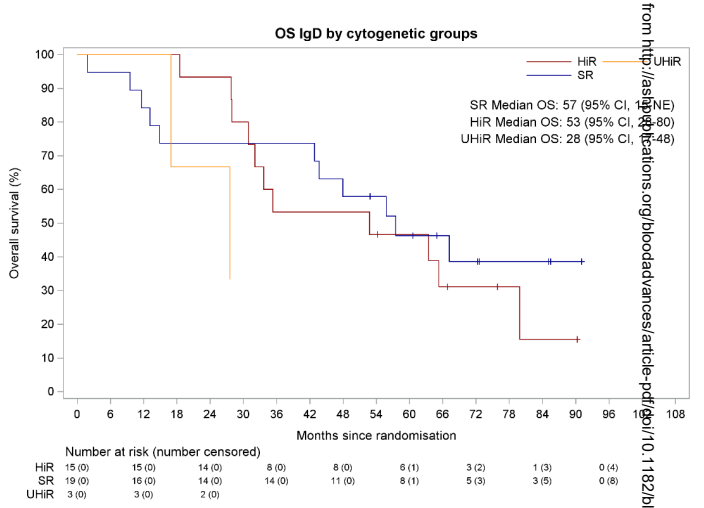
C



D



E



F