

Multiple Myeloma

RESEARCH REVIEW™

Making Education Easy

Issue 36 – 2020

In this issue:

- Real-life ixazomib-based frontline therapy in newly diagnosed MM
- Daratumumab + RVd for transplant-eligible newly diagnosed MM
- Mortality for MM inpatients with renal impairment undergoing autologous SCT
- Different *MAF* translocations confer similar prognosis in newly diagnosed MM
- Pomalidomide/cyclophosphamide/dexamethasone in relapsed/refractory MM
- Lenalidomide maintenance after second autologous SCT improves OS
- KRd vs. VRd in newly diagnosed MM intended for immediate autologous SCT
- Double vs. triple bortezomib regimens in MM with acute kidney injury due to cast nephropathy
- Maintenance vs. observation in transplant-ineligible, newly diagnosed MM
- Thrombosis in Myeloma IX and XI trial participants

Abbreviations used in this issue

CR = complete response
HR = hazard ratio
MM = multiple myeloma
OS = overall survival
PFS = progression-free survival
RCT = randomised controlled trial
SCT = stem-cell transplantation
VGPR = very good partial response
VTE = venous thromboembolism



Welcome to issue 36 of Multiple Myeloma Research Review.

The use of ixazomib-based induction therapy in routine clinical practice is relatively uncommon for several reasons, so the first study for this issue is useful, as it describes the effectiveness and safety of such treatment in a multicentre cohort of real-world patients. US research has confirmed that dialysis inpatients with MM who undergo autologous SCT with high-dose melphalan are at increased risk of dying. Another included study, an RCT, found no benefit of adding cyclophosphamide to bortezomib and dexamethasone in terms of renal recovery for patients with initial myeloma cast nephropathy and acute kidney injury not requiring dialysis. This issue concludes with a report of VTE risk in participants treated with immunomodulatory drugs for MM in the Myeloma IX and XI RCTs.

We hope you find the selected research in this issue interesting and helpful in your everyday practice. Please don't hesitate to send us your thoughts and suggestions.

Kind regards,

Dr Ken Romeril

kennethromeril@researchreview.co.nz

Dr Henry Chan

henrychan@researchreview.co.nz

Ixazomib-based frontline therapy in patients with newly diagnosed multiple myeloma in real-life practice showed comparable efficacy and safety profile with those reported in clinical trial

Authors: Li J et al.

Summary: The real-life effectiveness and safety of ixazomib-based induction therapy was reported for an observational cohort of 85 patients with newly diagnosed MM. IRd (ixazomib, lenalidomide, dexamethasone) was used in 44.7% of the patients, ixazomib plus dexamethasone in 29.4%, and ixazomib, dexamethasone plus doxorubicin, cyclophosphamide, thalidomide or daratumumab in 25.9%. The ixazomib induction regimens were given for a median of six cycles (range 1–20). Ten patients also received ixazomib maintenance. The overall response rate was 95.3%, including VGPR or better and CR rates of 65.9% and 29.5%, respectively, with a median time to response of 30 days. The different ixazomib-based regimens were associated with similar response rates. Median PFS was not reached. The grade ≥ 3 adverse event rate was 29.4%, and the discontinuation rate due to adverse events was 15.3%; there were no cases of grade 3–4 peripheral neuropathy.

Comment (KR): It seems surprising that the use of ixazomib has not been more widely taken up considering the convenience of a once-daily oral regimen. Despite accessing a lot of centres, this study only accrued 85 newly diagnosed MM patients. Similar to the TOURMALINE trial in which a number of us were involved, the drug was well tolerated and there was a low incidence of neuropathy. The drug is a useful alternative option in the newly diagnosed MM group. IRd is a useful combination in the relapsed setting as well.

Reference: *Ann Hematol* 2020;99:2589–98

[Abstract](#)

Independent commentary by Dr Ken Romeril, FRACP, FRCPA

Ken is a haematologist specialising in malignant haematology. He trained in Christchurch, Sydney and Southampton, and is currently at the Bowen Icon Cancer Centre. Ken has a particular interest in translational myeloma research and genetics. He is involved in clinical trials, is the current Chair of Myeloma New Zealand, a former chair of the ALLG Myeloma Sub-Committee, and is the NZ representative on the International Myeloma Working Group, which has around 200 members.



RACP MyCPD Program participants can claim one credit per hour
(maximum of 60 credits per year) for reading and evaluating Research Reviews.

FOR MORE INFORMATION [CLICK HERE](#)

Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma

Authors: Voorhees PM et al., for the GRIFFIN Trial Investigators

Summary: Autologous SCT-eligible patients with newly diagnosed MM were randomised to a standard regimen of four cycles of Rvd (lenalidomide, bortezomib dexamethasone) induction, autologous SCT, two cycles of Rvd consolidation and 26 cycles of lenalidomide maintenance with (n=103) or without (n=103) the addition of daratumumab (induction, consolidation and maintenance) in the phase 2 GRIFFIN trial. The addition of daratumumab to Rvd was associated with a significantly greater stringent CR rate at the end of consolidation treatment (42.4% vs. 32.0%; odds ratio 1.57 [95% CI 0.87, 2.82]) and at median follow-up of 22.1 months (62.6% vs. 45.4% [p=0.0177]), and a greater minimal residual disease negativity rate (51.0% vs. 20.4% [p<0.0001]). The respective 24-month PFS rates in the Rvd and Rvd plus daratumumab arms were 89.8% and 95.8%. There was a greater incidence of grade 3–4 haematological adverse events, but not infections, in the Rvd plus daratumumab group.

Comment (KR): The GRIFFIN trial is regarded as a pivotal trial where daratumumab was added to an already effective upfront treatment for transplant-eligible myeloma patients. It showed a statistically significant endpoint reached with a stringent CR by the end of the post-SCT consolidation. It was a phase 2 study, so was not intended to evaluate small patient subgroups such as those with high-risk cytogenetics. The positive results will support the rationale for the ongoing phase 3 PERSEUS study, which will investigate the use of subcutaneous administration.

Reference: *Blood* 2020;136:936–45

[Abstract](#)

Inpatient mortality of patients with multiple myeloma and renal impairment undergoing autologous stem cell transplantation

Authors: Mohyuddin GR et al.

Summary: Inpatient mortality and trends over time were investigated for patients from the US National Inpatient Sample with MM and renal impairment undergoing autologous SCT with high-dose melphalan. From a weighted estimate of 47,253 inpatient admissions, weighted totals of 45 and 1709 patients underwent peritoneal dialysis and haemodialysis, respectively, during autologous SCT with high-dose melphalan. The risk of inpatient mortality was increased by 20.5% and 13.8% for peritoneal and haemodialysis patients undergoing transplantation, respectively, even after other comorbidities were considered (odds ratio 6.193 [CI 3.585, 10.701]). The risk of inpatient mortality decreased significantly from 15.6% in 2009 to 5% in 2014 for patients with end-stage renal disease undergoing autologous SCT with high-dose melphalan.

Comment (KR): It is often a difficult decision to perform an autotransplant on an MM patient with significant renal impairment. A reduction in the melphalan dose is often indicated, but most centres have performed transplants successfully on fully dialysis-dependent patients. The mortality in this paper was quite high peaking at around 20%, which would indicate that careful patient selection is mandatory, as this level of mortality is really unacceptable.

Reference: *Eur J Haematol* 2020;105:571–7

[Abstract](#)



This Research Review has been endorsed by The Royal New Zealand College of General Practitioners (RNZCGP) and has been approved for up to 1 CME credit for the General Practice Educational Programme (GPEP) and Continuing Professional Development (CPD) purposes. You can record your CME credits in your [RNZCGP Dashboard](#)



Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please [CLICK HERE](#).

DARZALEX® + Vd provides longer mPFS in 1PL multiple myeloma^{1*}

78% reduction in risk of disease progression or death^{1*}

*27mths with Darzalex + Vd vs 7.9mths with Vd alone (HR 0.22, p<0.0001)

Vd: bortezomib + dexamethasone mPFS = median Progression Free Survival HR = Hazard Ratio 1PL: 1 prior line of therapy

Reference: 1. Mateos et al. Clin Lymphoma Myeloma Leuk. 2019 Oct 9;S2152-2650(19)32010-5. doi: 10.1016/j.clml.2019.09.623. Online ahead of print. **DARZALEX® (daratumumab) 20 mg/mL concentrate for solution for infusion. Indications:** Newly diagnosed multiple myeloma in combination with: bortezomib, thalidomide and dexamethasone (ASCT eligible); bortezomib, melphalan and prednisone, or lenalidomide and dexamethasone (ASCT ineligible). Multiple myeloma after at least one prior therapy in combination with: bortezomib and dexamethasone, or lenalidomide and dexamethasone. Monotherapy after at least three prior therapies including a proteasome inhibitor (PI) and immunomodulatory agent or refractory to both PI and immunomodulatory agent. **Dosage (Adults ≥18 years):** 16 mg/kg body weight administered as an intravenous infusion at appropriate initial infusion rate following dilution with 0.9% Sodium Chloride – see full Data Sheet for dosing schedules for combination therapy and monotherapy and concomitant medications pre- and post-infusion. DARZALEX should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions (IRRs) if they occur. Incremental escalation of the infusion rate should be considered only in absence of infusion reactions. **Contraindications:** Severe hypersensitivity (e.g. anaphylactic reaction) to daratumumab or excipients. **Precautions:** Before starting combination therapy, also refer Data Sheet of medicines used with DARZALEX. **Infusion-related reactions (IRR):** DARZALEX can cause serious IRR, including anaphylactic reactions. Monitor patients throughout infusion and post-infusion period. If anaphylactic reaction or life-threatening (Grade 4) IRR, permanently discontinue DARZALEX and institute appropriate emergency care. Pre-medicate with antihistamines, antipyretics and corticosteroids to reduce risk of IRR. Interrupt infusion for IRR of any severity. Institute medical management/supportive treatment as needed. For Grades 1-3 reactions, reduce infusion rate when re-starting infusion. See full Data Sheet for pre- and post-infusion medications. **Neutropenia/Thrombocytopenia:** Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Dose delay may be required. Consider supportive care with transfusions or growth factors. **Hepatitis B Virus (HBV) reactivation:** Screen all patients before initiation. If positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following end of treatment. If HBV reactivation occurs, suspend treatment with DARZALEX and any concomitant steroids, chemotherapy, and institute appropriate treatment. **Effect on laboratory tests: Interference with indirect antiglobulin test (indirect Coombs test):** Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after last infusion. Type and screen patients prior to initiation. For planned transfusion, notify blood transfusion centres. If emergency transfusion, non-cross-matched ABO/RhD-compatible RBCs can be given. **Interference with determination of complete response:** Daratumumab can be detected on serum protein electrophoresis and immunofixation assays. Interference can impact determination of complete response and disease progression in some patients with IgG kappa myeloma protein. **Excipients:** Each 5 mL and 20 mL vial of DARZALEX contains 9.3 mg and 37.3 mg sodium, respectively. **Pregnancy:** Category C. Women of reproductive potential should use contraception during and for 3 months after cessation of DARZALEX treatment. For combination with lenalidomide or thalidomide, patients (male and female) should adhere to pregnancy prevention programme of these medicines. **Breastfeeding:** Discontinue breast-feeding or discontinue DARZALEX therapy, taking into account the benefits and risks to mother and child. **Adverse Reactions:** Infusion reactions, anaphylactic reactions, peripheral sensory neuropathy, infections, hepatitis B virus reactivation, diarrhoea, nausea, vomiting, constipation, fatigue, asthenia, pyrexia, influenza, pneumonia, bronchitis, upper respiratory tract infection, nasopharyngitis, muscle spasms, chills, headache, cough, dyspnoea, pulmonary oedema, anaemia, thrombocytopenia, neutropenia, lymphopenia, leukopenia, peripheral oedema, atrial fibrillation, back pain, paraesthesia, arthralgia, pain in extremity, musculoskeletal chest pain, decreased appetite, dehydration, hyperglycaemia, hypocalcaemia, urinary tract infection, hypertension, pancreatitis, sepsis. See full Datasheet for other Adverse Effects. **Medicine Classification:** Prescription Medicine **Presentation:** 20 mg/mL concentrate for solution for infusion available as 100 mg daratumumab/5 mL vial and 400 mg daratumumab/20 mL vial. **Storage Conditions:** Unopened vials: Store at 2–8°C, protect from light (store in original package). After dilution: Use as soon as possible. Solution may be stored 2–8°C (protect from light) up to 24 hours prior to use, followed by 15 hours (including infusion time) at room temperature 15°C–25°C and room light. DARZALEX is an unfunded medicine – a prescription charge will apply. Before prescribing, please review full Data Sheet (available from www.janssen.com/newzealand/our-medicines). Janssen-Cilag (New Zealand) Ltd, 507 Mount Wellington Hwy, Mount Wellington, Auckland 1060, New Zealand. Material date of preparation: Jul 2020. CP-164081. NA 12133

For more information, please go to <http://www.medsafe.govt.nz>

Independent Content: The selection of articles and writing of summaries and commentary in this publication is completely independent of the advertisers/ sponsors and their products.

Privacy Policy: Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time.

Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

Research Review publications are intended for New Zealand health professionals.

Continuous
REVLIMID
Maintenance
After ASCT in ndMM¹

Revlimid®
(lenalidomide) capsules

**SURVIVAL
BENEFIT***²

PHARMAC
FUNDED³

***Proven OS benefit,**
including in patients with CR/VGPR to ASCT

vs. no maintenance therapy.

In the ITT population (n=460; median OS: **9.5 years** vs. 7.0 years,
HR: 0.61; 95% CI: 0.46–0.80; p=0.0004) and in patients achieving CR/VGPR
(n=281/460; median OS: **not reached** vs. 6.7 years, logHR: 0.66; 95% CI: 0.28–1.00)

All data at a median follow-up of 7.6 years²

REVLIMID® is a funded medicine for Relapsed Refractory Multiple Myeloma and post ASCT Maintenance, Special Authority criteria apply.

REVLIMID® is an unfunded medicine for Newly Diagnosed Transplant Ineligible Multiple Myeloma and a prescription charge will apply. REVLIMID® is a Prescription Medicine.

Before prescribing Revlimid® (lenalidomide) please [click here](#) to review full Data Sheet.

Do not use Revlimid during pregnancy. Teratogenic Effects: Revlimid (lenalidomide) is structurally related to thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Women should be advised to avoid pregnancy whilst taking Revlimid (lenalidomide), during dose interruptions, and for 4 weeks after stopping the medication.

Abbreviations: ASCT: autologous stem cell transplant; CI: confidence interval; CR: complete response; HR: hazard ratio; ITT: intention to treat; ndMM: newly diagnosed multiple myeloma; OS: overall survival; VGPR: very good partial response.

References: 1. REVLIMID® New Zealand Data Sheet. 2. Holstein SA, et al. *Lancet Haematol* 2017;4:e431–42. 3. Pharmac. New Zealand Government. Online Pharmaceutical Schedule - May 2020, Lenalidomide. <https://www.pharmac.govt.nz/wwwtr/ScheduleOnline.php?osq=Lenalidomide&code=C2501074035> (accessed May 2020).

Celgene | Bristol Myers Squibb
Company

Celgene Pty Ltd, Level 15/60 City Rd, Southbank, Vic 3006, Australia. www.celgene.com.au
NZ Registered Office: Celgene Ltd, PO Box 3035, Wellington 6011, New Zealand. Tel: 0800 526 529.
*Registered Trademark PM-NZ-REV-0010. CLIN4597. TAPS No. NA 11967. Last revised: May 2020.

For more information, please go to <http://www.medsafe.govt.nz>

Different MAF translocations confer similar prognosis in newly diagnosed multiple myeloma patients

Authors: Goldman-Mazur S et al.

Summary: The prognostic impact of the MAF translocations t(14;16) and t(14;20) was assessed in 254 patients; 87.8% had the t(14;16) and 12.2% had the t(14;20) translocations. The respective median PFS durations for patients with the t(14;16) and t(14;20) translocations were 16.6 months and 24.9 months (p=0.28), and the respective median OS durations were 54.0 months and 49.0 months (p=0.62). Median OS duration was longer for patients who underwent double autologous SCT than for those who underwent single autologous SCT (107.0 vs. 60.0 months [p<0.001]). Patients with ISS stage 3 had inferior OS (HR 1.89 [95% CI 1.24, 3.19]).

Comment (KR): There have now been several studies that highlight the adverse prognosis related to the MAF translocations, and in particular, t(14;16). Personal experience has found very short survivals of <12 months in some patients with this adverse genetic signature. This large group of MAF translocation patients indicates that t(14;20) patients should also be considered to have a high-risk signature.

Reference: *Leuk Lymphoma* 2020;61:1885–93
[Abstract](#)

m eloma
new zealand

Myeloma NZ is a foundation in NZ to provide a deeper level of support for those who are affected by multiple myeloma. If patients or their loved one have been diagnosed with multiple myeloma, Myeloma NZ can help them learn about treatment options and point them to information and services to help them cope with the disease.

www.multiplemyeloma.org.nz/

Claim your
CPD points
for reading
Research Reviews

FIND OUT MORE

A phase II study of pomalidomide, daily oral cyclophosphamide, and dexamethasone in relapsed/refractory multiple myeloma

Authors: Van Oekelen O et al.

Summary: This open-label, phase 2 trial examined the addition of metronomic cyclophosphamide to a pomalidomide and dexamethasone regimen in relapsed/refractory MM. A total of 33 patients with lenalidomide-refractory disease (55% also proteasome inhibitor-refractory) received 28-day cycles of pomalidomide 4 mg/day, cyclophosphamide 50mg twice daily and weekly dexamethasone. The overall response rate was 73%, the median PFS duration was 13.3 months, and the median OS duration was 57.2 months. Grade 3–4 toxicities were primarily haematological, but were manageable.

Comment (KR): The prognosis of patients with relapsed/refractory disease is quite limited, and we need to find better strategies for patients already exposed to immunomodulatory drugs and the proteasome inhibitors. Pomalidomide has both tumouricidal and antiangiogenic properties. The addition of cyclophosphamide is known to overcome resistance, and so these triplet regimens have been previously tried with various dosing regimens. Metronomic therapy with daily low-dose cyclophosphamide and a 1-week respite was used to reduce myelosuppression. The results were excellent, with a respectable OS duration of around 57 months.

Reference: *Leuk Lymphoma* 2020;61:2208–15

[Abstract](#)

Lenalidomide maintenance after second autologous stem cell transplant improves overall survival in multiple myeloma

Authors: Modi D et al.

Summary: Outcomes were described for a retrospective group of 111 adults with MM who had undergone a second autologous SCT, after which they had been followed for a median of 58 months. For patients who received no maintenance (n=73), maintenance lenalidomide ≤ 15 mg daily (n=23) and maintenance subcutaneous bortezomib 1.3 mg/m² every 2 weeks (n=15), the respective 3-year PFS rates were 11.2%, 29.9% and 0%, and the respective 3-year OS rates were 58.5%, 83.3% and 67.5%; lenalidomide maintenance provided significantly superior PFS and OS compared with no maintenance (respective HRs 0.46 and 0.25 [p=0.009 for both]).

Comment (HC): The data from this single centre retrospective review are interesting. Firstly, they revealed an increasing number of patients undergoing second autologous SCT in more recent years (2012–2018). This is somewhat surprising, as published data on the effectiveness of second autologous SCT at the time of relapse are not that much better than novel drug combinations after one prior line of treatment: Rd, median PFS 14.1 months (MM009 and MM010); KRd, median PFS 29.6 months (ASPIRE); DRd, median PFS not reached (POLLUX); DVd, median PFS not reached (CASTOR). Secondly, the study manages to show a survival benefit for lenalidomide maintenance over no maintenance after second transplantation. This is consistent with the published data in the frontline setting, and reinforces the benefit of continuous treatment over fixed-period strategies. Lastly, the benefit of bortezomib maintenance appears to be only modest on multivariate analysis, even after adjusting for the second-line therapy used.

Reference: *Leuk Lymphoma* 2020;61:1877–84

[Abstract](#)

New Zealand Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our [CPD page](#).

Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE)

Authors: Kumar SK et al.

Summary: The open-label, phase 3 ENDURANCE trial randomised patients with standard- or intermediate-risk MM to receive 12 3-week induction cycles of KRd (carfilzomib, lenalidomide, dexamethasone; n=545) or VRd (bortezomib, lenalidomide, dexamethasone; n=542), after which they underwent a second randomisation stratified by induction therapy to divide them into ongoing maintenance or fixed-duration 2-year maintenance lenalidomide regimens. The primary outcome of PFS did not differ significantly between the KRd versus VRd arms after median follow-up of 9 months (34.6 vs. 34.4 months; HR 1.04 [95% CI 0.83, 1.31]); median OS had not been reached in either group. KRd induction was associated with more grade 3–4 treatment-related nonhaematological adverse events than VRd, including hyperglycaemia, dyspnoea and thromboembolic events, and also more treatment-related deaths (11 vs. 2).

Comment (HC): To fully appreciate the results from this study, one must also review the supplementary data in depth. On the surface, it appears that KRd was no better than VRd in the frontline setting with similar PFS and OS. However, the study design and data interpretation may have muddied the water. Firstly, only about half of the patients completed the 36-week induction (61.6% in the KRd arm and 43.3% in the VRd arm). There was a numerically greater number of patients in the VRd arm who stopped treatment due to adverse events/complications, whilst the reported grade 3–4 toxicities were actually fewer in the VRd arm. There was also a higher number of patients in the VRd arm who withdrew to go on to alternative therapy (17.7% vs. 13.7%), including autologous SCT, which could certainly affect the survival data. Although the authors did attempt to address this by censoring these patients at the time of alternative therapy in a sensitivity analysis (supplementary data), this is unlikely to be able to fully compensate for any potential bias. Lastly, although the authors also presented the data specifically for those under the age of 70 years (similar to the overall results), as the study design did not mandate frontline transplantation, this result may not be applicable to other centres where frontline autologous SCT is the standard of care for transplant-eligible patients.

Reference: *Lancet Oncol* 2020;21:1317–30

[Abstract](#)

[CLICK HERE](#)

to read previous issues of Multiple Myeloma Research Review



NEW

Precision Oncology

RESEARCH REVIEW™

This review is a unique NZ publication that aims to provide readers with topical and accessible information on the fast-developing and exciting field of precision or personalised cancer treatments. The review includes significant recent research in the field, focusing on tests, techniques and treatments that are relevant to the NZ setting.

SIMPLY CLICK

I am a Health Professional

to send us an e-mail and we'll do the rest

RESEARCH REVIEW™
Making Education Easy — Since 2006

Randomized trial comparing double versus triple bortezomib-based regimen in patients with multiple myeloma and acute kidney injury due to cast nephropathy

Authors: Bridoux F et al., for the MYRE study group

Summary: After receiving symptomatic measures and high-dose dexamethasone, patients with initial myeloma cast nephropathy and acute kidney injury not requiring dialysis were randomised to receive bortezomib plus dexamethasone with (n=92) or without (n=92) cyclophosphamide; participants with a <50% reduction in serum free light chain levels after three cycles could have their chemotherapy reinforced. Compared with bortezomib plus dexamethasone, the addition of cyclophosphamide did not significantly change the 3-month renal response rate (primary endpoint; relative risk 0.87 [p=0.46]) or the VGPR or better rate (0.76 [p=0.10]), and the numbers of participants who achieved a serum free light chain level of ≤500 mg/L after the first cycle of chemotherapy were similar (67 vs. 69 participants). Serious adverse events occurred in 30 bortezomib plus dexamethasone recipients and 40 bortezomib, dexamethasone plus cyclophosphamide recipients, and at 12 months, nine and ten from the respective arms had died (six and four from myeloma progression and zero and three from infections).

Comment (HC): Renal impairment is a common complication from myeloma, but there is a lack of published RCT data specifically on this patient group. The data from this French study show that in patients with true cast nephropathy, rather than acute renal impairment from prerenal failure or hypercalcaemia related to myeloma, over 40% of them will still have an estimated glomerular filtration rate of <40 mL/min at 12 months, despite receiving treatment for their myeloma. Unsurprisingly, patients who achieved a deeper response were more likely to experience recovery in renal function, and these patients who had a renal response had a trend towards better OS. The primary aim of this study was to assess renal response, which was not improved with the addition of cyclophosphamide to bortezomib-dexamethasone. However, renal response is just one aspect to consider when managing these patients. The study does also show a trend for better time to next treatment for the triplet arm. The toxicity seen in the triplet arm may be due to the high intravenous dose of cyclophosphamide used, and a lower but greater frequency weekly dosing of cyclophosphamide, like CyBorD, may potentially be more tolerable.

Reference: *J Clin Oncol* 2020;38:2647–57

[Abstract](#)

Maintenance therapy in transplant ineligible adults with newly-diagnosed multiple myeloma

Authors: Balitsky AK et al.

Summary: This systematic review and meta-analysis included five RCTs (n=1139) comparing maintenance therapy with observation for newly-diagnosed transplant-ineligible MM. Compared with observation, maintenance therapy was associated with significantly improved PFS (HR 0.48 [95% CI 0.38, 0.62]), but not OS (0.96 [0.76, 1.2]); the respective certainties for these findings were high and moderate. Maintenance therapy was also associated with more adverse events than observation (very low-to-moderate certainty).

Comment (HC): The result of this study is more about the efficacy of lenalidomide maintenance than anything else, as that was the treatment used in the interventional arm of four of the five included studies. The result is also predominantly influenced by the UK MRC XI study, as it accounts for two-thirds of the patients. Therefore, similar to the published UK MRC XI result last year, the result from this meta-analysis shows improved PFS with maintenance, but no significant difference in OS. However, as most of these studies used immunomodulatory drug-based induction before switching to lenalidomide maintenance, questions remain as to whether lenalidomide maintenance will remain effective after proteasome inhibitor-based induction. Unfortunately, the GERMAIN study (included in this meta-analysis), which evaluated the role of lenalidomide maintenance after VMP induction, failed to recruit a meaningful number of patients to address this issue due to poor accrual and high dropout rates.

Reference: *Eur J Haematol* 2020;105:626–34

[Abstract](#)

Independent commentary by Dr Henry Chan

Dr Henry Chan is a consultant haematologist at North Shore Hospital in Auckland. Following completion of specialist training in clinical and laboratory haematology, he completed a clinical fellowship in multiple myeloma and lymphoma at Princess Margaret Cancer Centre in Toronto. He is currently actively involved in clinical research, registrar teaching and patient education.



Thrombosis in patients with myeloma treated in the Myeloma IX and Myeloma XI phase 3 randomized controlled trials

Authors: Bradbury CA et al. on behalf of the United Kingdom National Cancer Research Institute Haemato-oncology Clinical Studies Group

Summary: This report provides a pooled prospective evaluation of thrombotic risk in patients with newly diagnosed MM treated with immunomodulatory agent-based induction therapy (thalidomide and lenalidomide) in the Myeloma IX (n=1936) and XI (n=4358) clinical trials. VTE rates were significantly lower in the Myeloma IX trial with CTD (cyclophosphamide, thalidomide, dexamethasone) induction compared with CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone; 16.1% vs. 22.5%), but compared with melphalan/prednisolone induction, the VTE risk was increased 4-fold with attenuated CTD (16% vs. 4.1%, adjusted HR 4.25 [95% CI 2.5, 7.2]). VTE affected up to one fifth of patients, and lenalidomide- or thalidomide-based induction regimens conferred a similar thrombotic risk (Myeloma XI, CRD [cyclophosphamide, lenalidomide, dexamethasone] vs. CTD, 12.2% vs. 13.2%, adjusted HR 0.92 [95% CI 0.72, 1.18]). Although VTE rates dropped between the Myeloma IX and the Myeloma XI trials (CTD regimen, 16.1% vs. 13.2%; attenuated CTD, 16% vs. 10.7%) in response to implementation of an IMWG-guided thromboprophylaxis protocol in Myeloma XI, which meant thromboprophylaxis was used more regularly (80.5% vs. 22.3%), thrombotic events were still frequent. With the exception of an association between arterial events and reduced survival in Myeloma XI (adjusted HR 1.53 [95% CI 1.12, 2.08]), thrombotic events were not found to negatively impact on long-term survival or disease progression outcomes.

Comment (HC): The combined data from these two UK studies show that the risk of thrombosis in patients with myeloma receiving first-line treatment is as high as 13–15%, with the vast majority occurring during the first 6 months. Maintenance did not appear to increase the risk. A cross-study comparison between patients who received the same treatment across the two studies showed a numeric reduction in thrombosis rate in those who received thromboprophylaxis as per the current IMWG guidelines compared with those without mandated thromboprophylaxis (4.3 vs. 5.4 per 100 person-years). However, the rate remains high even with thromboprophylaxis, and further study is needed to see if more intense thromboprophylaxis is required, especially during the initial few months of treatment.

Reference: *Blood* 2020;136:1091–104

[Abstract](#)