

Multiple Myeloma

RESEARCH REVIEW™

Making Education Easy

Issue 34 – 2020

In this issue:

- Retrospective study of with t(14;16) MM
- RVD + daratumumab in transplant-eligible newly diagnosed MM
- Associations with OS in NZ MM patients
- VTE risk with lenalidomide regimens for MM despite thromboprophylaxis
- Factors predicting MM outcomes at different ages
- Significance of dysplastic haematopoiesis in newly diagnosed MM
- The genomic and transcriptomic landscape of double-refractory MM
- An anti-BCMA BITE induces responses in MM
- First-line VMP vs. Rd-R for transplant-ineligible MM
- Ibrutinib, bortezomib and dexamethasone in relapsed/refractory MM

Abbreviations used in this issue

BCMA = B-cell maturation antigen
BITE = bispecific T-cell engager
CR = complete response
FISH = fluorescence *in situ* hybridisation
HR = hazard ratio
ISS = International Staging System
MM = multiple myeloma
MRD = minimal residual disease
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
PI = proteasome inhibitor
SCT = stem-cell transplantation

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.

Welcome to issue 34 of Multiple Myeloma Research Review.

The t(14;16) translocation is present in only a small proportion of patients with newly diagnosed MM, but has been associated with adverse outcomes. The first paper in this issue describes the characteristics and outcomes for the largest reported cohort of such patients to date. Local research is included in the form of an evaluation of the impact of age, ethnicity and socioeconomic deprivation among NZ patients in the novel antimyeloma agent era. There is also research reporting that mutations in the genes for immunomodulatory agent and PI targets do not appear to be the main reason for resistance to these agents in MM, instead differential yet converging evolution of subclones is implicated. This issue concludes with a phase 2 trial of ibrutinib combined with bortezomib and dexamethasone for relapsed/refractory MM reporting that although clinical responses were seen, toxicity was an issue.

We hope you enjoy this update in MM research. We welcome any feedback or suggestions you wish to send us.

Kind regards,

Dr Ken Romeril

kennethromeril@researchreview.co.nz

Dr Henry Chan

henrychan@researchreview.co.nz

A multicenter retrospective study of 223 patients with t(14;16) in multiple myeloma

Authors: Goldman-Mazur S et al.

Summary: Characteristics and outcomes were described for a real-world retrospective cohort of 223 patients from 25 centres with t(14;16) MM. Renal impairment at presentation was recorded for 24% of the patients, and 56% had haemoglobin levels <10 g/dL at presentation. First-line therapy was an immunomodulatory drug plus PI combination for 35% of the patients, and 42% underwent autologous SCT. After median follow-up of 4.1 years, the respective median PFS and OS durations from first-line therapy were 2.1 years and 4.1 years. Age >60 years and revised ISS score 3 vs. 2 were significant predictors of worse OS (respective HRs 1.65 [95% CI 1.05, 2.58] and 2.59 [1.59, 4.24]).

Comment (KR): This paper was of interest to me because my personal experience with this uncommon translocation has not been good, and several patients have had very poor outcomes with survivals of only 6–9 months and they tended to be bortezomib-resistant. This study cohort was the largest ever accrued because it was multicentre. The OS of 4.1 years was much better than expected, but still well short of the usual OS that is currently being achieved in myeloma patients with novel agents.

Reference: *Am J Hematol* 2020;95:503–9

[Abstract](#)

Get your own copy of MULTIPLE MYELOMA RESEARCH REVIEW

Become one of Research
Review's 32,000 NZ members

SIMPLY CLICK

I am a Health Professional

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

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.



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

Authors: Voorhees PM et al.

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 MRD 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): This important study looked at the addition of daratumumab to RVD, which is currently considered the standard induction therapy in many countries but not in NZ at present. The daratumumab arm yielded very impressive stringent CR rates that continued to improve over time, as well as the rates of MRD negativity. The 24-month PFS rate of 95.8% in the daratumumab plus RVD arm was very impressive. Daratumumab is clearly an important addition to initial induction therapy and this is where it is most active. When it is being used locally at the moment as a single agent in heavily treated individuals, then the responses tend to be short-lived.

Reference: *Blood*; Published online April 23, 2020
[Abstract](#)



Continuous
REVLIMID
Maintenance
After ASCT in ndMM*

Revlimid®
(lenalidomide) capsules

SURVIVAL BENEFIT *2

PHARMAC
FUNDED

***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 years*

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/wwwtrs/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.



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](#).

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

Impact of age, sex, ethnicity, socio-economic deprivation and novel pharmaceuticals on the overall survival of patients with multiple myeloma in New Zealand

Authors: Chan HSH & Milne RJ

Summary: Incidences, prevalences and survival of NZ patients diagnosed with MM over the 2004–2016 period were reported. Over this time, there were increases in the crude incidence rate (from 5.42 to 8.47 per 100,000) and the age-standardised rate (from 4.01 to 5.28 per 100,000). At Dec 2016, the estimated prevalence was 37.8 per 100,000. Median OS duration increased between the 2004–2007 and 2012–2016 periods, from 34.8 to 50.7 months. Among patients aged >70 years, median OS duration increased from 19.4 to 28.6 months after bortezomib became publicly funded. For patients aged ≤70 years who did not undergo autologous SCT, median OS duration increased from 49.1 to 62.7 months, but there was no significant change for those who did not undergo autologous SCT. No increase in survival was seen for Māori/Pasifika people or those in the most deprived quintile after bortezomib became funded.

Comment (KR): This paper by Richard Milne and Henry Chan came about as a result of a restricted grant provided through Myeloma New Zealand to provide data for the extensive Burden of Disease report launched at Parliament in June 2019. It was a unique document and is the most detailed analysis on any type of cancer ever done in NZ. This paper in the Br J Haematol looks at some aspects of the data analysed and highlights the increased crude incidence rate that we have all noticed from our clinic lists. The fact that the median OS rate for patients aged over 70 years with the introduction of bortezomib use was significant emphasises that it is important to try and offer this drug to the older population. The novel agents have also had an impact on median OS in people aged under 70 years who do not get an autologous SCT. This paper and also the BOD report have also shown the adverse prognostic factors of Māori and Pasifika ethnicity. There is emerging evidence from a paper from Hilary Blacklock with data from the Monash Registry that the Māori population have an increased incidence of adverse FISH high-risk signatures, which could explain some of the poorer outcomes.

Reference: *Br J Haematol* 2020;188:692–700

[Abstract](#)

Venous thromboembolism risk with contemporary lenalidomide-based regimens despite thromboprophylaxis in multiple myeloma

Authors: Chakraborty R et al.

Summary: This was a systematic review with meta-analysis of 51 phase 1–3 clinical trials (n=9069) reporting the incidence of VTE (venous thromboembolism) in patients with newly diagnosed, relapsed or refractory MM treated with lenalidomide-based regimens and receiving thromboprophylaxis (mostly with aspirin, low-molecular-weight heparin or warfarin). In patients with median treatment durations of 2–34 cycles, the estimated pooled incidence of VTE was 6.2% or 1.2 events per 100 patient-cycles. The VTE event rate was lower in patients receiving lenalidomide and low-dose dexamethasone treatment compared with lenalidomide with low-dose dexamethasone and a PI (0.2 vs. 1.3 per 100 patient-cycles).

Comment (KR): The increased risk of VTE in lenalidomide-based regimens has been known for some time, but the approach to thromboprophylaxis has been varied with no standard approach. A risk-based strategy has been advocated taking into account previous thrombotic history, obesity, etc. The thrombotic risk appears to be higher during the induction phase and in the relapsed/refractory group. Thromboprophylaxis is not indicated in the maintenance setting, but if there is concomitant use of combination therapy with steroids and a PI, it would be worth considering.

Reference: *Cancer* 2020;126:1640–50

[Abstract](#)



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/

VELCADE®
(bortezomib)

Look forward again

VELCADE (bortezomib). VELCADE is fully funded, Special Authority criteria apply. **Indications:** Untreated multiple myeloma unsuitable for high dose chemotherapy, in combination with melphalan and prednisone. Multiple myeloma, received at least one prior therapy, have progressive disease. As part of combination therapy, for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma. **Dose and method of use:** 1.3 mg/m² may be administered intravenously at a concentration of 1 mg/mL as a 3–5s bolus injection or subcutaneously at a concentration of 2.5 mg/mL, see full Data Sheet for dosing schedule; reduce or withhold dose with haematological toxicity or neuropathy. Retreatment may be considered for patients who had responded to treatment with VELCADE; see full Data Sheet. VELCADE is for intravenous or subcutaneous use only. Intrathecal administration has resulted in death. **Contraindications:** Hypersensitivity to bortezomib, boron or mannitol. **Precautions:** DO NOT ADMINISTER INTRATHECALLY, peripheral neuropathy, hypotension, cardiac disorders, seizures, thrombocytopenia, gastrointestinal adverse events, pulmonary disorder, posterior reversible encephalopathy syndrome, seizures, tumour lysis syndrome, hepatic events, hepatic impairment, renal impairment, fertility, lactation, driving or operating machinery, pregnancy, lactation, children, frequently monitor Complete Blood Counts, see full Data Sheet. **Interactions with other drugs:** Inhibitors or inducers of CYP isozymes (in particular to CYP 3A4) eg ketoconazole, ritonavir, rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort. Oral hypoglycaemics. Caution patients with concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, statins), or with a decrease in blood pressure. **Adverse events:** Infections, pyrexia, gastrointestinal disorders, haematological disturbances, peripheral neuropathy, hypotension, haematoma, headache, decreased appetite, general psychiatric disorders, dyspnoea, rash, blurred vision, vertigo, myalgia; fatigue, pyrexia, tumour lysis syndrome (uncommon), Stevens-Johnson Syndrome, toxic epidermal necrolysis, pulmonary disorders, intestinal obstruction, progressive multifocal leukoencephalopathy, very rare cases with unknown causality of John Cunningham (JC) virus infection resulting in PML and death, anaphylactic reaction, thrombotic microangiopathy, others, see full Data Sheet. **Presentation:** VELCADE is a Prescription Medicine containing bortezomib 1 mg or 3.5 mg per single dose vial. **Date of Preparation:** 13 November 2018. Please review full Data Sheet before prescribing, available at www.medsafe.govt.nz or on request from Janssen-Cilag (New Zealand) Ltd, PO Box 62185, Sylvia Park 1644, Auckland, New Zealand. Material Preparation Date: Jun 2019. MKT-VEL-NZ-0006. TAPS NA 8996. INSIGHT 9282

Janssen
PHARMACEUTICAL COMPANIES OF
Johnson & Johnson

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

The relative importance of factors predicting outcome for myeloma patients at different ages

Authors: Pawlyn C et al.

Summary: These authors report the relative contributions of disease and patient factors to MM outcomes relative to patient age. Based on analysis of 3894 patients with newly diagnosed MM enrolled in the phase 3 Myeloma XI clinical trial, they found that age changed the relative impact of different factors on survival. In contrast to younger patients, elderly patients had reduced PFS and OS as well as decreased renal function. The impact of molecular risk factors such as chromosomal abnormalities was more pronounced in younger patients, with survival in elderly patients determined more by physical functioning at diagnosis than degree of myeloma disease. Performance status was uniformly a predictor of outcome across all ages.

Comment (KR): This very large MRC trial looked at the effect mainly of lenalidomide maintenance, but the authors have drilled down in this paper to look at such variables as the revised ISS and also the molecular risk that occurs with age. The median age of the patients in the trial was 68 years, and the authors found that patients over the age of 80 years had particularly bad outcomes. The patients had an OS of only 40% compared with 80% in patients aged <60 years. They observed that high-risk signatures like t(4;14) were only found in 5% of older patients, which is very similar to my own studies in the older group, but 1q amplification was more common. Also renal function deterioration was a significant predictor of poor outcome. These data are of interest because often older patients are excluded from clinical trials.

Reference: *Leukemia* 2020;34:604–12

[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.

Biological and clinical significance of dysplastic hematopoiesis in patients with newly-diagnosed multiple myeloma

Authors: Da Silva Maia CA et al.

Summary: Prospective screening of bone marrow samples from 285 PETHEMA/GEM2012MENOS65 trial participants revealed that 33 exhibited MDS-associated phenotypic alterations. In a group of 67 patients, targeted sequencing revealed that clonal haematopoiesis was detected in a greater proportion of patients with versus without MDS-associated phenotypic alterations (50% vs. 22%); the most frequently mutated genes were *TET2* and *NRAS*. In 80% of 86 evaluable patients, MDS-associated phenotypic alterations persisted (if present at baseline) or remained absent (if absent at baseline) after autologous SCT. It was infrequent for MDS-associated mutations to emerge after high-dose therapy. Patients with MDS-associated phenotypic alterations had altered haematopoiesis and regulatory T-cell distribution in the tumour microenvironment. The presence of monocytic MDS-associated phenotypic alterations at diagnosis was associated with increased risk of haematological toxicity and was independently associated with inferior PFS and OS (respective HRs 1.5 and 1.7 [p values 0.02 and 0.01]).

Comment (HC): After analysing samples from various prospective studies, this Spanish group found a significant number of patients with a myelodysplastic phenotype on EuroFlow at the time of diagnosis (11.6%). Clinically, these patients were generally older, had a greater disease burden and experienced more treatment-related neutropenia and anaemia. Biologically, these patients were found to have a higher frequency of clonal haematopoiesis, expanded myeloid/erythroid precursors, reduced lymphoid precursors, maturation arrest in the immature neutrophil stages, reduced γ - δ -naïve T-cells and expansion of CCR7-negative regulatory T-cells. Interesting as these data may be, the causality of many of these findings remains uncertain. Could the myelodysplastic phenotype be just a marker of clonal haematopoiesis that has perpetuated the expansion of the malignant plasma cell clone via immune dysregulation? What was clinically interesting is their observation of an inferior survival associated with myelodysplastic phenotype that was independent of ISS, lactate dehydrogenase level and FISH in those who did not have immunomodulatory drug maintenance. This may be less relevant now for transplant-eligible patients with lenalidomide maintenance becoming the standard of care, but this may potentially be useful in patients who are transplant-ineligible if continuous immunomodulatory drug-based treatment becomes available.

Reference: *Blood*; Published online April 16, 2020

[Abstract](#)

Integrative analysis of the genomic and transcriptomic landscape of double-refractory multiple myeloma

Authors: Ziccheddu B et al.

Summary: This research included 42 patients with MM refractory to both PIs and immunomodulatory agents – 40 underwent whole-exome sequencing and 27 underwent RNA sequencing. More mutations including subclonal mutations were detected than had been identified at diagnosis, and the mutational landscape differed from that previously described for samples taken at diagnosis. The most frequently inactivated pathway was TP53 (45% of patients), but point mutations in genes associated with immunomodulatory drug resistance were rare and always subclonal. Refractory patients exhibited a unique mutational signature linked to alkylating agent exposure. RNA sequencing revealed that neither treatment nor mutations influenced clustering, which was influenced by karyotypic events. A cluster with both amp(1q) and del(13) characterised by *CCND2* upregulation and also overexpression of *MCL1* was described, representing a novel target for experimental treatments. High-risk features were detected in 65% of the patients; however, survival was predicted only by 1q amplification.

Comment (HC): Despite focusing on a cohort of patients who were resistant to PIs and immunomodulatory drugs, the authors were unable to detect any specific pattern to fully explain the mechanism of drug resistance. Although abnormalities in the immunomodulatory drug resistance and proteasome subunit genes were found, they were rare and only found in the subclones. Meanwhile, gene expression analysis also failed to show a significant difference in expression levels of genes associated with resistance to PIs or immunomodulatory drugs. They did find enrichment of 1q amplification and biallelic inactivation of the TP53 pathway. However, how these changes have led to drug resistance remain elusive. It is therefore assumed that the development of drug resistance is the result of convergent evolution, where each subclone acquires its ability via different mechanisms. This highlights the difficulties in finding a single druggable target to overcome treatment resistance and the importance of using a multidrug regimen, especially in patients with advanced disease.

Reference: *Blood Adv* 2020;4:830–44

[Abstract](#)

[CLICK HERE](#) to read previous issues of Multiple Myeloma Research Review

Anti-B-cell maturation antigen BiTE molecule AMG 420 induces responses in multiple myeloma

Authors: Topp MS et al.

Summary: In this phase 1, first-in-human study, 42 patients with relapsed/refractory MM received up to ten 6-week cycles of dose-escalated intravenous AMG 420 (an anti-BCMA BiTE [bispecific T-cell engager]) 0.2–800 µg/day by 4-week continuous infusions; a median of one cycle was given with only three participants receiving the full 10 cycles. Discontinuations were due to disease progression (n=25), adverse events (n=7), death (n=4) and withdrawn consent (n=1). Two participants were still on treatment at the time of reporting. The serious adverse event rate was 48%, and the response rate was 31%. At the maximum tolerated dosage (400 µg/day), the ORR was 70%, including five MRD-negative CRs, one partial response and one very good partial response. All responses at the maximum tolerated dose were observed during cycle one, and responses lasted for a median of 9 months.

Comment (HC): This is a first-in-human phase 1 study on a BiTE that binds to CD3 and BCMA. The high rate of serious adverse events (48%) is concerning, with 33% of the patients experiencing infections (mostly grade 3, but there were two deaths) and five patients developing liver impairment (including one death). Polyneuropathy also appears to be increased, while cytokine-release syndrome was mostly mild and manageable. The ORR of 70% amongst the ten patients who received 400 µg/day in the dose-escalation and expansion cohorts is not that dissimilar to other treatments that target BCMA (e.g. belantamab mafodotin and anti-BCMA CAR [chimeric antigen receptor] T-cell therapy). However, due to the size of the molecule, the treatment is given as a continuous infusion over 4 weeks in a 6-weekly cycle. This, in conjunction with the toxicities, may limit the widespread adoption of this drug in clinical practice in the future. A half-life extended anti-BCMA BiTE that can be administered once weekly (AMG701) is currently being trialled, and hopefully this will have a better toxicity profile.

Reference: *J Clin Oncol* 2020;38:775–83

[Abstract](#)



First-line therapy with either bortezomib-melphalan-prednisone or lenalidomide-dexamethasone followed by lenalidomide for transplant-ineligible multiple myeloma patients

Authors: Larocca A et al.

Summary: Pooled data from the GIMEMA-MM-03-05 and EMN01 trials, both of which randomised patients with newly diagnosed MM to receive bortezomib, melphalan, prednisone (VMP; n=257) or lenalidomide plus dexamethasone induction followed by lenalidomide maintenance (Rd-R; n=217), were included in subgroup analyses. PFS and OS did not differ between the two treatments among standard-risk participants, but high-risk VMP recipients had lower probabilities of progression and death than Rd-R recipients (respective HRs 0.54 and 0.73). Standard-risk participants aged >75 years derived less benefit from VMP than from Rd-R (respective HRs for PFS and OS, 0.96 and 1.81).

Comment (HC): Recently, the regimen of Rd-R, where patients receive lenalidomide monotherapy following an initial phase of Rd induction, is gaining popularity. However, similar to other lenalidomide-based regimens, this has never been compared head-to-head with an established bortezomib-based regimen in the frontline setting for elderly patients. The results from these two European studies show that VMP and Rd-R are equivalent in most standard-risk patients. However, VMP appears to be better for patients with high-risk cytogenetics, while there is a trend for better OS for Rd-R in those older than 75 years. The results from this study highlight the need for a more tailored approach for transplant-ineligible patients and the importance of cytogenetics even in this patient group. The previous one-size-fits-all approach for transplant-ineligible patients is outdated, and more research is needed for a risk- and frailty-adapted approach.

Reference: *Haematologica* 2020;105:1074–80

[Abstract](#)

A phase 2 study of ibrutinib in combination with bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma

Authors: Hajek R et al.

Summary: Patients with relapsed/refractory MM who had received 1–3 prior therapies received an ibrutinib, bortezomib and dexamethasone combination regimen in this phase 2 open-label trial; 74/76 enrolled participants received ≥1 dose of the study regimen. Median follow-up was 19.6 months, after which the median PFS duration was 8.5 months and the median OS duration had not been reached. The ORR was 57% with a median response duration of 9.5 months. The grade 3–4 adverse event rate was 73% and the fatal adverse event rate was 15%. Major haemorrhages occurred in 5% of participants, resulting in one death. Enrolment into the trial was suspended.

Comment (HC): Despite preclinical data demonstrating the increased expression of Bruton's tyrosine kinase in myeloma cells and possible association with drug resistance via increased expression of efflux pumps, the results from the majority of the early-phase studies on ibrutinib in myeloma have been disappointing. Gastrointestinal toxicity appears to be common across the various ibrutinib combinations (Jamil F et al. *Blood* 2018;132[Suppl 1]:1948 – ASH 2018), and it is no exception with bortezomib in this study. The rate of infection in this study is unacceptably high, including eight fatal infections. In view of the biology and drug action, the increased risk of infection, especially those of the respiratory tract, may be the result of marked hypogammaglobulinaemia induced by the treatment. Unfortunately, the authors have not presented any data on the participants' immunoglobulin levels, leaving one to wonder whether regular immunoglobulin replacement could have potentially improved the safety profile of this combination.

Reference: *Eur J Haematol* 2020;104:435–42

[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](#).

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](#)