Multiple Myeloma RESEARCH REVIEW™

Making Education Easy

Issue 32 – 2019

In this issue:

Abbreviations used in this issue
BCMA = B-cell maturation antigen
MM = multiple myeloma
ORR = overall response rate
OS = overall survival
PD-1/PD-L1 = programmed cell death (ligand)-1
PFS = progression-free survival
SCT = stem-cell transplantation
SNP = single nucleotide polymorphism

NZMA New Zealand Medical Association

myeloma new zealand

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Welcome to issue 32 of Multiple Myeloma Research Review.

This issue begins with research investigating the influence of SNPs (single nucleotide polymorphisms) of the *CRBN* gene on the risk of adverse effects associated with thalidomide-based chemotherapy for MM. We have also included important real-life research supporting the VRD (bortezomib, lenalidomide, dexamethasone) induction regimen with high OS rates compared with VCD (bortezomib, cyclophosphamide, dexamethasone), but unfortunately, we are still not able to offer VRD to our patients. There is also research on response kinetics for MM in the era of novel agents showing that slow and gradual responses are more favourable. Results from the KEYNOTE-183 and -185 trials of pembrolizumab, pomalidomide and dexamethasone in MM are also presented.

We would also like to express great thanks to Dr David Simpson for his valuable expertise and input into Multiple Myeloma Research Review over the years. It was a privilege to be associated with David over 31 issues, and we wish him well in his new role.

Please remember, your comments and feedback are always welcome.

Kind regards,

Dr Ken Romeril
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Dr Henry Chan
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Polymorphisms in the promotor region of the *CRBN* gene as a predictive factor for peripheral neuropathy in the course of thalidomide-based chemotherapy in multiple myeloma patients

Authors: Mlak R et al.

Summary: This research investigated the influence of specific genetic factors on treatment complications to thalidomide-based chemotherapy for MM. Adverse effects to front-line thalidomide, cyclophosphamide and dexamethasone treatment were analysed for 82 patients and correlated to SNPs of the *CRBN* gene. A multivariate analysis showed a significant correlation between the presence of the *CRBN* CC genotype (rs1672753) and significantly increased risks for peripheral polyneuropathy and diarrhoea (respective odds ratios 14.29 and 16.67). *CRBN* genotypes AA (rs6768972) and TT (rs1672753) showed a protective effect against the risk of constipation (respective odds ratios 0.003 and 0.004).

Comment (KR): In our clinical practice, we have all seen patients who seem to develop neuropathy on thalidomide within a very short time and often under 6 months. This elegant study shows us the genetic factors that predispose patients to this early neuropathy and also gastric side effects. We will hopefully be able to pretest our patients for this abnormality in the future, but it is likely to be some time before it becomes an available test. The trend is for thalidomide to be used for much shorter durations.

Reference: Br J Haematol 2019;186:695–705
Abstract

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Research Review publications are intended for New Zealand health professionals.

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.

Clinical efficacy of daratumumab, pomalidomide, and dexamethasone in patients with relapsed or refractory myeloma: utility of re-treatment with daratumumab among refractory patients

Authors: Nooka AK et al.

Summary: The utility of retreatment with daratumumab among refractory patients, as well as in naïve patients, was retrospectively analysed in 34 patients with MM treated with combination daratumumab, pomalidomide and dexamethasone. All the patients had received prior therapy with immunomodulatory drugs and proteasome inhibitors, and they were divided into cohorts based on their prior exposure to daratumumab and pomalidomide. Cohort 1 (n=12) was comprised of patients naïve to both daratumumab and pomalidomide. Cohort 2 (n=22) included patients who were refractory to daratumumab and/or pomalidomide when treatments were received individually, and included a subgroup (cohort 3) of 12 patients who were refractory to both agents. Patients naïve to daratumumab and pomalidomide treatment had an ORR of 91.7% and included four stringent complete responses. At a median 41 months of follow-up, this group had not reached median PFS duration. Cohort 2 had an ORR of 40.9% and a median PFS duration of 3.2 months. Cohort 3 had an ORR of 33.3% to the combination therapy, with a PFS duration of 2.5 months.

Comment (KR): This is a small study that has been around for a while and was actually first presented at ASH 2016 in San Diego. The extremely good PFS benefit certainly shows the benefit of adding a monoclonal antibody to any regimen, and this even worked in people who had exhibited prior refractoriness to both daratumumab and pomalidomide. It is an attractive triplet that may mean that a quadruplet regimen may not be required.

Reference: Cancer 2019;125:2991–3000
Abstract

Response to first cycle is the major predictor of long-term response to lenalidomide and dexamethasone therapy in relapsed and refractory multiple myeloma: can we spare patients the toxicity and costs of additional agents?

Authors: Gassiot S et al.

Summary: Patients with relapsed or refractory MM who had a good response (PFS >24 months) to lenalidomide plus dexamethasone salvage therapy were identified and characterised in this research; 227 patients with evaluable data from three tertiary-care hospitals were identified. A multivariate analysis revealed that the main independent predictor of PFS >24 months was achieving a partial response after the first therapy cycle, which, along with standard-risk cytogenetics, also predicted a higher complete response rate. The only baseline characteristic associated with long-lasting response was prior plasma-cell dyscrasia. Significant prognostic factors for poorer OS were high-risk cytogenetics and no history of monoclonal gammopathy of undetermined significance, whereas there was a trend for improved OS in patients who had received only one prior therapy.

Comment (KR): This is a nice 'real world' study that is relevant to our current NZ practice. It clearly shows that the quality of response to the first cycle is a major predictor of a good long-term response. The fact that a high-risk genetic signature is a negative prognostic factor should guide clinicians to looking at some supplementary more active therapy, such as bortezomib. The recent lifting of restrictions on the use of bortezomib may allow clinicians to augment treatment in such high-risk cases as the t(4;14), which we know is more susceptible to bortezomib.

Reference: Clin Lymphoma Myeloma Leuk 2019;19:585–92
Abstract

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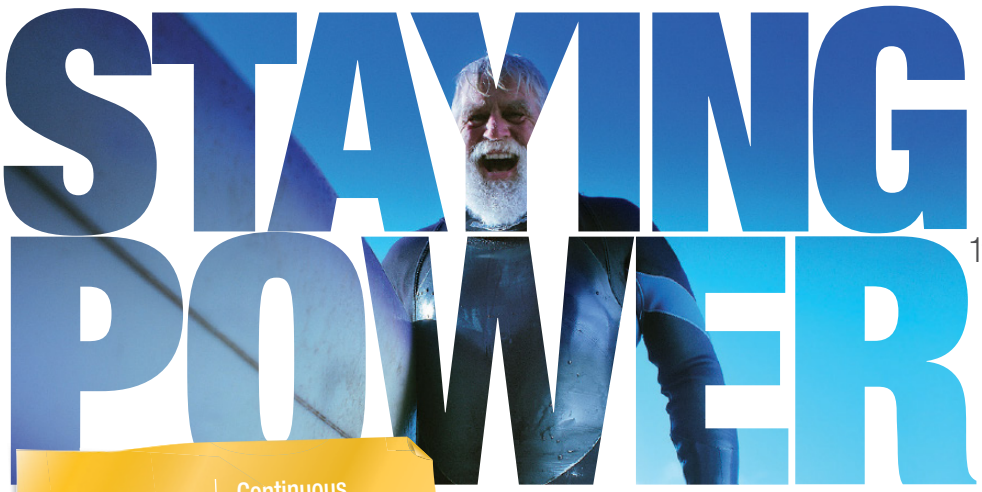

*FIRST: Frontline Investigation of Revlimid and dexamethasone vs. Standard Thalidomide trial. **Continuous:** treatment until disease progression or intolerance; **dex:** dexamethasone; **MPT:** melphalan, prednisone, thalidomide; **ndMM:** newly diagnosed multiple myeloma; **OS:** overall survival; **Rd:** REVLIMID/dexamethasone; **VGPR:** very good partial response. Before prescribing REVLIMID (lenalidomide) please refer to following page. TAPS No. NA 11216

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Upfront bortezomib, lenalidomide, and dexamethasone compared to bortezomib, cyclophosphamide, and dexamethasone in multiple myeloma

Authors: Uttervall K et al.

Summary: This was a retrospective analysis of patients treated with first-line VCD or VRD, with or without subsequent high-dose treatment and autologous SCT; 351 patients received VRD with and 213 without high-dose treatment, and 71 received VRD with and 46 without high-dose treatment. Compared with VCD, use of VRD was associated with: i) a higher ORR (98% vs. 88% [p<0.001]), including among those who did not receive high-dose treatment (98% vs. 79% [p<0.001]); ii) a higher 18-month PFS rate overall (88% vs. 63%), in the subgroup who did not receive high-dose treatment (82% vs. 32%) and the subgroup who did (91% vs. 73%); and iii) a higher 18-month OS rate (95% vs. 89% [p=0.048]).

Comment (KR): This is an important comparison because the study compares our standard induction regimen of CyBorD (VCD) with VRD, which is very popular in the US but which we cannot offer to our patients. I understand that VRD has been approved by the PBAC in Australia recently. This quite large study yielded a very impressive ORR of 98%. The 18-month analysis showed that the VRD-treated group had superior survival also. We need to be able to offer this sort of induction regimen to our patients, and it is yet another unmet clinical need.

Reference: Eur J Haematol 2019;103:247–54
Abstract

Once-weekly *versus* twice-weekly carfilzomib in patients with newly diagnosed multiple myeloma

Authors: Bringhen S et al.

Summary: These researchers analysed pooled phase 1–2 trial data to compare efficacy and safety of once-weekly versus twice-weekly dosing of carfilzomib in patients with newly diagnosed MM. The trials comprised 121 transplant-ineligible participants who received nine induction cycles of carfilzomib, cyclophosphamide and dexamethasone followed by carfilzomib maintenance. Sixty-three participants received a once-weekly schedule of carfilzomib 70 mg/m^2 and 58 received a twice-weekly dose of 36 mg/m^2. No significant difference was seen between the once-weekly and twice-weekly dosing groups for median PFS (35.7 vs. 35.5 months [p=0.26]), 3-year OS (70% vs. 72% [p=0.50]) or grade 3–5 haematological adverse events (24% vs. 30% [p=0.82]).

Comment (KR): This is the ARROW study that has been extensively referenced by speakers at recent meetings. The results clearly show that the more convenient once-weekly approach using a single high dose of carfilzomib prolonged the median PFS of relapsed MM patients. Many clinicians in the US have been using the once-weekly approach for some time now, and the ARROW phase 3 trial results confirm that it is a reasonable approach to deliver a more convenient schedule.

Reference: Haematologica 2019;104:1640–7
Abstract

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The impact of response kinetics for multiple myeloma in the era of novel agents

Authors: Yan Y et al.

Summary: The relationship between response kinetics and outcome was explored for 626 trial participants with newly diagnosed MM assigned to either immunomodulatory drug-based or PI-based therapy. While there was an association between depth of response and better outcome, survival was significantly worse for participants whose best response was ≤3 months versus those who responded later, and for those who achieved rapid complete remission versus those who achieved a gradual partial remission. Participants who achieved gradual and sustained remission experienced longer median OS duration than those who achieved a rapid and transient response (126 vs. 30 months). The effects of response patterns on survival were confirmed in participants at different disease stages and cytogenetic risks, including transplant-eligible participants and those achieving a range of response depths.

Comment (HC): The data from this study are interesting as they suggest that patients who achieved their best response within 3 months of treatment had a worse long-term prognosis than those who responded more slowly. This pattern was consistently seen across all response subgroups in their cohort, and appears to be contradictory to our experience in other haematological malignancies, such as acute leukaemia where a rapid response is often associated with a favourable outcome. The hypothesis is that a rapid response may simply reflect the high proliferative activity of the malignancy plasma cells, and it is this increase in proliferative activity that can lead to early disease relapse and selection of treatment-resistant clones. How should these results be interpreted in clinical practice? Clinicians may want to monitor those who achieved an early response more closely and consider having a higher threshold for changing treatment for those with a more gradual response.

Reference: Blood Adv 2019;3:2895–904
Abstract

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Revlimid® (lenalidomide) Capsules Minimum Data Sheet. Indications: Revlimid is indicated for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation. Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma patients whose disease has progressed after one therapy. **Contraindications and precautions:** (Pregnancy Risk Category X) – Pregnancy; women of childbearing potential unless all of the conditions of the i-access® Program are met; hypersensitivity to lenalidomide or excipients. To avoid the risk of foetal exposure, Revlimid is only available under a restricted distribution program (i-access®). **Other precautions:** Breast feeding. Second Primary Malignancies (SPMs): in clinical trials of Revlimid an imbalance in the incidence of SPMs between treated and control groups has been observed. The expected benefit of Revlimid and the risk of SPMs should be considered before initiating treatment; patients should be evaluated for SPMs before and during treatment. Myocardial infarction. Venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event). If patient experiences thromboembolic events, discontinue Revlimid treatment and start anticoagulant therapy, with treatment reinitiation at original dose once stable and depending upon a benefit-risk assessment. Anticoagulation therapy should then be continued during the course of Revlimid treatment. Neutropenia, thrombocytopenia (dose reduction may be required). Peripheral neuropathy. Tumour Lysis Syndrome (TLS) and Tumour Flare Reaction (TFR). Consider interruption or discontinuation of Revlimid for Grade 2-3 skin rash. Permanently discontinue Revlimid for angioedema, Grade 4 rash, exfoliative or bullous rash, or suspected Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis or drug reaction eosinophilia and system symptoms (DRESS). Patients with prior history of grade 4 rash associated with thalidomide should not receive Revlimid. Atrial fibrillation. Impaired thyroid function. Lactose intolerance. Hepatic disorders; monitoring recommended. Chronic Lymphocytic Leukaemia (CLL) and Revlimid: In a clinical trial of first-line treatment of patients with CLL, Revlimid was associated with increased risk of death - not recommended for use in CLL outside of controlled clinical trials. No experience in treating children and adolescents (0-18 years). Serious adverse events more common in patients greater than 65 years of age. Monitor renal function in patients with renal impairment; dosage adjustment may be required. **Interactions:** Use with caution with erythropoietic agents, hormone replacement therapy or other agents that increase the risk of thrombosis. Use with caution when coadministering with myelosuppressive agents. Oral contraceptive efficacy may be reduced during treatment. Efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone. Monitor warfarin concentration. Monitor digoxin concentration. Increased risk of rhabomyolysis with statins. Adverse Drug Reactions (MM and MDS) VERY COMMON: pneumonia; bronchitis; bacterial, viral and fungal infections (including opportunistic infections); upper respiratory tract infection; neutropenias; thrombocytopenia; anaemia, leukopenias; decreased appetite; hypokalaemia; hyperglycaemia; hypocalcaemia; insomnia; depression; peripheral neuropathies (excluding motor neuropathy); dizziness; tremor; dysgeusia; headache; cataracts; blurred vision; venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism); dyspnoea; epistaxis; diarrhoea; vomiting; nausea; constipation; abdominal pain; dyspepsia; rash; pruritus, dry skin; hyperhidrosis; musculoskeletal and connective tissue pain and discomfort; bone pain; muscle spasms; arthralgia; myalgia; renal failure (including acute); pyrexia; oedema (including peripheral); asthenia; influenza-like illness syndrome (including pyrexia, cough, rhinitis, myalgia, musculoskeletal pain, headache and rigours); fatigue; weight decreased COMMON: sepsis, sinusitis, hypothyroidism; febrile neutropenia; pancytopenia; dehydration; hypomagnesaemia; iron overload; hypokalaemia; hypocalcaemia; hypophosphataemia; diabetes mellitus; hyperglycaemia; hyponatraemia; gout; lethargy; syncope; cerebrovascular accident; myocardial infarction (including acute); atrial fibrillation; tachycardia; cardiac failure (including congestive); hypertension; hypotension; haematoma; respiratory distress; dry mouth; toothache; abnormal liver function tests; cholestasis; erythema; muscular weakness; chest pain; fall; contusion; squamous cell carcinoma POST-MARKETING:SJS; toxic epidermal necrolysis; TLS; TFR; hepatic failure (incl. acute); hepatitis toxic; cytolytic hepatitis; cholestatic hepatitis; mixed cytolytic/cholestatic hepatitis; acute graft-versus-host disease (after allogeneic transplant); pancreatitis; pneumonitis;hyperthyroidism; viral reactivation (such as hepatitis B virus or herpes zoster); solid organ transplant rejection; DRESS. **Dosage and administration:** Multiple myeloma (MM): recommended starting dose is 25 mg orally once daily on days 1-21 of repeated 28-day cycles; for recommended dose of dexamethasone please see Data Sheet. In MM dosing is continued or modified based upon clinical and laboratory findings, and to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicities judged to be related to Revlimid. Dose adjustments are recommended at the start of therapy for patients with moderate or severe impaired renal function, or end stage renal disease (refer to Dosage and Administration in Data Sheet). Revlimid (5 mg, 10 mg, 15 mg and 25 mg capsules) should be taken at about the same time each day swallowed whole (not opened, broken or chewed), preferably with water one hour before or two hours after food. Please review the Revlimid® (lenalidomide) Data Sheet for the full dosage and administration recommendations. Min Data Sheet V3.1.1) 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 NZ-REV0123. BB-CLIN3612. TAPS No. NA 11216. 30/07/19. **References: 1.** Facon T, et al. Blood 2018;131:301-10. **2.** REVLIMID® Product Information. **3.** Benboubker L, et al. N Eng J Med 2014;371:906-17. **4.** Hulin C, et al. J Clin Oncol 2016;34:3609-17.

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Daratumumab and dexamethasone is safe and effective for triple refractory myeloma patients

Authors: Boyle EM et al., on behalf of the IFM2014-04 investigators

Summary: Final results were reported from the Intergroupe Francophone du Myélome 2014-04 (Etoile du Nord) trial, in which 57 evaluable patients with triple-relapsed/refractory MM received infusions of daratumumab plus weekly dexamethasone until disease progression or unacceptable toxicity. The respective ORR and clinical benefit rate were 33% and 48%, with a very good partial response or better rate of 8.8%. Median time to response was 4 weeks, and responders had a longer median PFS duration than those with minimal or stable disease (6.6 vs. 3.7 months). The median OS duration for all participants was 16.7 months, for responders it was 23.23 months and for participants with progressive disease it was 2.97 months. Infusion-related reactions occurred at an incidence of 37%, but there were no resultant dose reductions or permanent treatment discontinuations.

Comment (HC): Albeit with the limitations of a cross-study comparison, the addition of dexamethasone to daratumumab does not appear to yield any substantial improvement in response rate or PFS compared with the published data on daratumumab monotherapy (Lokhorst et al, 2015; Lonial et al, 2016; Usmani et al, 2016). Meanwhile, the infection rate was noticeably higher with the addition of dexamethasone with 18.5% of the patients experiencing a grade 3 or higher infection despite many patients receiving prophylaxis. Altogether, it is difficult to justify the use of daratumumab-dexamethasone over daratumumab monotherapy.

Reference: Br J Haematol 2019;187:319–27
Abstract

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Bortezomib consolidation following autologous transplant in younger and older patients with newly diagnosed multiple myeloma in two phase III trials

Authors: Straka C et al.

Summary: These authors conducted a *post hoc* analysis of data from two phase 3 trials in patients with newly diagnosed MM to assess how age and treatment factors influence the efficacy of bortezomib consolidation on PFS after autologous SCT. One of the trials had enrolled 202 participants aged 18–60 years and the other had enrolled 155 participants aged 61–75 years, and both randomised the participants to four 35-day cycles of bortezomib 1.6 mg/m^2 on days 1, 8, 15 and 22 or observation only. There was no significant difference between the bortezomib consolidation versus observation arms for median PFS duration among participants aged 18–60 years (33.6 vs. 29.0 months [p=0.3599]), but this was significantly longer for bortezomib recipients aged 61–75 years (33.4 vs. 26.4 months [p=0.0073]). Outcomes for the younger and older participants who received prior treatment of differing intensity appeared to be equalised by bortezomib consolidation after autologous SCT.

Comment (HC): As expected, the data from these two phase 3 studies (one for patients aged 18–60 years and the other for patients aged 61–75 years) show an improvement in depth of response with bortezomib consolidation after autologous SCT. Although an improvement in PFS was noted in the 61- to 75-year age group and not the younger cohort, this disparity in observation between the two age groups is likely due to the substantial difference in bortezomib exposure prior to consolidation (70% in the 18- to 60-year group and 22% in the 61- to 75-year group). The final multivariate analysis did however confirm bortezomib consolidation as a positive prognostic factor for PFS, but this did not translate into an OS benefit. With this, the debate regarding the role of post-autologous SCT consolidation continues, but it does appear across the literature that the benefit of consolidation depends on the intensity of induction treatment given.

Reference: Eur J Haematol 2019;103:255–67
Abstract

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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/m^2 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, nitrofurantion, 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 1mg 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

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Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naive multiple myeloma (KEYNOTE-185)

Authors: Usmani SZ et al., for the KEYNOTE-185 Investigators

Summary: Transplant-ineligible adults with newly diagnosed MM (ECOG performance status of 0 or 1) were randomised to receive 28-day cycles of oral lenalidomide 25mg on days 1–21 and oral dexamethasone 40mg on days 1, 8, 15 and 22 with (evaluable n=149) or without (evaluable n=145) intravenous pembrolizumab 200mg every 3 weeks in the open-label, phase 3 KEYNOTE-185 trial. The trial was terminated early due to a mortality imbalance between the study arms. Median PFS (primary endpoint) was not reached in either group, with no significant between-group difference for the estimated 6-month PFS rates (p=0.75). The respective serious adverse event rates in the pembrolizumab and non-pembrolizumab arms were 54% and 39%, the most common being pneumonia (6%) and pyrexia (5%) in the pembrolizumab arm and pneumonia (6%) and sepsis (1%) in the non-pembrolizumab arm. There were six treatment-related deaths among pembrolizumab recipients and two among lenalidomide and dexamethasone only recipients.

Reference: Lancet Haematol 2019;6:448–58
Abstract

Pembrolizumab plus pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma (KEYNOTE-183)

Authors: Mateos M-V et al., for the KEYNOTE-183 Investigators

Summary: Adults with MM refractory to ≥2 lines of therapy that excluded pomalidomide (ECOG performance status 0 or 1) were randomised to receive 28-day cycles of oral pomalidomide 4mg on days 1–21 and oral dexamethasone 40mg on days 1, 8, 15 and 22 with (n=125) or without (n=124) intravenous pembrolizumab 200mg every 3 weeks in the open-label, phase 3 KEYNOTE-183 trial. The trial was terminated, with median follow-up of 8.1 months, due to an unfavourable risk-benefit assessment. For the respective pembrolizumab and non-pembrolizumab arms, the median PFS durations were 5.6 months and 8.4 months, with no significant difference for the estimated 6-month PFS rates (p=0.98), and the median OS durations were not reached and 15.2 months (p=0.95). The respective serious adverse event rates in the pembrolizumab and non-pembrolizumab arms were 63% and 46%. There were four treatment-related deaths among pembrolizumab recipients and none among the pomalidomide and dexamethasone only recipients.

Reference: Lancet Haematol 2019;6:459–69
Abstract

Comment (HC): These two KEYNOTE studies were halted by the US FDA in July 2017 after noting a risk signal. The published data from both studies show a higher rate of serious adverse events, discontinuations of treatment due to adverse events and treatment-related deaths in the pembrolizumab arm. In KEYNOTE-183, neutropenia and thrombocytopenia were more frequent in the pembrolizumab arm, and the increased treatment-related death rate was due to neutropenic sepsis, myocarditis, Stevens-Johnson syndrome and unknown cause. In KEYNOTE-185, the rates of pyrexia, pneumonia, sepsis, acute renal injury and pulmonary embolism were higher for the pembrolizumab arm, whilst the causes of treatment-related death were cardiac arrest, cardiac failure, myocarditis, large intestine perforation, pneumonia and pulmonary embolism. Despite promising preclinical and early-phase data, PD1/PD-L1 inhibition for the management of myeloma does not appear to be a viable option in the near future.

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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.

Selective targeting of multiple myeloma by B cell maturation antigen (BCMA)-specific central memory CD8+ cytotoxic T lymphocytes: immunotherapeutic application in vaccination and adoptive immunotherapy

Authors: Bae J et al.

Summary: These authors reported on research that identified novel engineered peptides specific to BCAM: $BCMA_{72–80}$ (YLMFLLRKI) and $BCMA_{54–62}$ (YILWTCLGL). These peptides showed improved affinity/stability to HLA-A2 compared with their native peptides, and they induced highly functional BCMA-specific cytotoxic T-cells with increased activation (CD38, CD69) and costimulatory (CD40L, OX40, GITR) molecule expression. The heteroclitic $BCMA_{72–80}$-specific cytotoxic T-cells exhibited polyfunctional Th1-specific immune activities against MM, which correlated with Tetramer-positive and memory CD8-positive cytotoxic T-cell expansion, and when treated with an immune agonist or a checkpoint inhibitor, they showed increased immune function, mainly via central memory cytotoxic T-cells.

Comment (HC): In this preclinical study, this group in Boston showed that tumour specific CD8-positive cytotoxic T-lymphocytes can be induced by repeatedly stimulating the CD3-positive T-lymphocytes with antigen-presenting cells pulsed with an engineered heteroclitic BCMA peptide. In addition to having antimyeloma activities, the resulting population of T-lymphocytes was also found to include myeloma-specific memory T-lymphocytes. The self-renewing capability of these memory T-lymphocytes may potentially allow this approach to provide long-lasting immunity against myeloma. This may potentially be a more robust, less labour-intensive and cheaper immunotherapeutic strategy than other existing methods. Plans are already underway for these cancer vaccines to be tested in clinical trials, but their results will be some years away.

Reference: Leukemia 2019;33:2208–26
Abstract

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